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Rosiglitazone and Hepatic Failure

To the Editor: In this issue, Forman and colleagues (1) report on a patient who developed severe liver dysfunction while receiving rosiglitazone. Although we have not had the opportunity to review the manuscript of this case report in advance of publication, we would like to point out some important facts about the case. Our company was informed of this patient's clinical status at the time the events occurred. We immediately requested, and were able to obtain, entire medical records from both the community hospital where the patient initially presented and from the university hospital where the patient was transferred. These records were extensively reviewed by us and other physicians at SmithKline Beecham Pharmaceuticals and were also sent out to three highly respected hepatologists who have particular expertise in drug-induced liver disease: Neil Kaplowitz (Los Angeles, California), James Lewis (Washington, D.C.), and Paul Watkins (Chapel Hill, North Carolina). These hepatologists independently concluded that this patient's liver injury was probably the result of ischemia and not rosiglitazone.

Among the many observations that support this conclusion, it should be noted that the patient had significant valvular heart disease, chronic atrial fibrillation, congestive heart failure, and a history of vascular disease previously requiring coronary artery bypass graft surgery and endarterectomy. On admission to the community hospital, he was noted to have a junctional rhythm, and the admitting physician commented that the patient was "showing signs of peripheral hypoperfusion." The patient was admitted to the intensive care unit at this hospital, and an arterial line and Swann-Ganz catheter were inserted. The patient's course in the intensive care unit at the initial hospital was complicated by hypotension (blood pressure, 76/59 mm Hg, with a cardiac output of 3.24 L/min) and hypoxia (PO₂, 48 mm Hg). In addition, the pattern and time course of biochemical abnormalities are characteristic of ischemic hepatitis, particularly the decrease in serum aspartate aminotransferase level from greater than 11 000 U/L to normal within 9 days. Such high and rapidly normalizing serum aminotransferase values are unusual for most cases of drug-induced liver disease and have not been characteristic of troglitazone (2). Indeed, our consultants each stated that they would also believe that the liver injury was probably due to ischemia even if this patient had been receiving troglitazone.

In the rosiglitazone clinical trials program, the rate of liver chemistry abnormalities did not differ between patients receiving rosiglitazone and those receiving placebo. To date, rosiglitazone has been prescribed to more than 150 000 patients. Although we acknowledge the natural deficiencies of postmarketing reporting, the controlled clinical trials experience is thus far predictive of the rosiglitazone safety experience in the marketplace.

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1. Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. *Ann Intern Med.* 2000;132:118-21.
2. Watkins PB, Whitcomb RW. Hepatic dysfunction associated with troglitazone. *N Engl J Med.* 1998;338:916-7.

Cross-Cultural Primary Care

To the Editor: We commend Carrillo and colleagues for developing a curriculum addressing cultural issues in primary care (1). The increasing diversity of patients in the United States necessitates formal teaching about cultural influences on medical practice.

However, we urge the authors to look beyond patients to health professionals as another source of cultural differences affecting patient care. Because nearly all receive western-oriented bioscientific training, health professionals practicing in U.S. hospitals and clinics may not perceive significant cultural differences among colleagues—even when those colleagues come from different ethnic groups or nationalities.

Yet such cultural differences certainly exist and can exert a powerful effect on patient care. In studying a western-style Kenyan mission hospital, we discovered that the Euroamerican and Kenyan health professionals there differed drastically over patient autonomy and used different approaches to manage conflicts between patients' wishes and welfare. The Euroamericans allowed competent adults to make potentially harmful decisions about their treatment, but the Kenyans did not (2). Other authors have also documented cultural differences among health professionals concerning what is extraordinary care, what quality of life is worth living, what should be told to patients, and who should make decisions about treatment (3, 4). These examples convince us that western-style medical education does not erase a health professional's core, culturally determined beliefs about health, illness, and proper relations between professionals and patients (5).

With increasing cultural diversity among health professionals in the United States, cross-cultural conflicts affecting patient care are bound to arise among health professionals. Physicians must be able to recognize those conflicts and resolve them without harm to patients.

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2. Perkins HS, Supik JD, Hazuda HP. Cultural differences among health professionals: a case illustration. *J Clin Ethics.* 1998;9:108-17.
3. Surbone A. Truth telling to the patient. *JAMA.* 1992;268:1661-2.
4. Sehgal AR, Weisheit C, Miura Y, Butzlaff M, Kielstein R, Taguchi Y. Advance directives and withdrawal of dialysis in the United States, Germany, and Japan. *JAMA.* 1996;276:1652-6.
5. Hartog J, Hartog EA. Cultural aspects of health and illness behavior in hospitals. *West J Med.* 1983;139:910-6.

To the Editor: Carrillo and colleagues' article (1) makes a valuable and significant contribution to patient care in cross-cultural settings. However, we believe that the authors missed a crucial component of effective, patient-based approaches to cross-cultural care, namely the patient's spiritual and religious perspective.

In our experience, the patient's religious worldviews inform virtually every aspect of the explanatory model the authors describe. Patients do make sense religiously of life experience, including illness: This perspective is often a crucial dimension of culture.

Religion is more than a stress management technique. No religion ignores the meaning of affliction, suffering, illness, and healing. Likewise, no physician should ignore or overlook the patient's religious or spiritual understanding of the world. Although these understandings may be familiar to patients, they remain unfamiliar to many physicians and social scientists. Hence, they are easily overlooked or deemed insignificant.

Rather than adding a new module called "understanding the patient's religious or spiritual context," we suggest integrating this perspective into each of the existing modules. The objective would be to illustrate how answers to each of the questions delineated may, from a patient's perspective, be deeply informed by his or her religious worldview.

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Reference

1. Carrillo JE, Green AR, Betancourt JR. Cross-cultural primary care: a patient-based approach. *Ann Intern Med.* 1999;130:829-34.

In response: We appreciate and welcome these insightful comments. Cross-cultural medical education is attracting great interest while rapidly evolving. It is crucial to have open and ongoing dialogue on the content and approach to curricula that attempt to improve care to socioculturally diverse populations. We agree with Drs. Perkins and Hazuda on the importance of looking "beyond patients to health professionals." The brief description of our "basic concepts" module mentions that "...participants reflect on their own cultures and how these influence their personal perspectives on illness and health care." Although this is simply stated, we pay great attention to this issue through various exercises, including participant testimonials, case discussions, and the exploration of "biomedicine" as culture. Furthermore, our "core cultural issues" module emphasizes the importance of understanding both the patient's and provider's perspective on issues such as patient autonomy and the perceived role of the physician.

Drs. Plotnikoff and Barnes are correct to state that the patient's spiritual and religious perspective is a critical dimension of culture and an important component of cross-cultural care. We integrate this perspective into our entire curriculum, especially in our "meaning of the illness" module. Several of our case discussions deal with different religious perspectives, and the concept of illness as "God's will" frequently arises when participants present their own cases. In addition, the patient's religious and spiritual views are explored as part of their "social context," and we did not intend to minimize the importance of this facet of a patient's life and culture.

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Prostacyclin for Secondary Pulmonary Hypertension

To the Editor: We read with interest McLaughlin and colleague's report on the use of prostacyclin to treat secondary pulmonary hypertension (1). Primary causes of precapillary pulmonary hypertension in their series included congenital heart disease, collagen vascular disease, sarcoidosis, distal thromboem-

Table. Pulmonary Vascular Resistance before and after Prostacyclin Infusion

Patients	Pulmonary Vascular Resistance before Prostacyclin Infusion	Pulmonary Vascular Resistance after Prostacyclin Infusion
	dynes/sec per cm ⁵	
1	253	199
2	242	114
3	293	248
4	214	152

bolic disease, and portopulmonary hypertension. Sickle cell disease is also a cause of secondary pulmonary hypertension (2, 3). During the cardiac catheterization diagnosis of pulmonary hypertension in four adult patients with sickle cell anemia, our cardiology colleague tested them for response to prostacyclin. The results are listed in the **Table**.

In three of the four patients, prostacyclin decreased pulmonary vascular resistance, suggesting that pulmonary hypertension secondary to sickle cell disease may be responsive to this drug.

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References

1. McLaughlin VV, Genthner DE, Panella MM, Hess DM, Rich SH. Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: a case series. *Ann Intern Med.* 1999;130:740-3.
2. Sutton LL, Castro O, Cross DJ, Spencer JE, Lewis JF. Pulmonary hypertension in sickle cell disease. *Am J Cardiol.* 1994;74:626-8.
3. Castro O. Systemic fat embolism and pulmonary hypertension in sickle cell disease. *Hematol Oncol Clin North Am.* 1996;6:1289-303.

In response: Mild pulmonary hypertension is not uncommon in the setting of sickle cell disease and may be present in up to two thirds of patients, along with left atrial and left ventricular dilatation. In fact, pulmonary hypertension may be related to elevated left-sided filling pressures or a high output state from anemia. Although Kaur and colleagues did not give the individual data for the four patients with sickle cell disease, such as the mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output, we are given the pulmonary resistance. Of note, the pulmonary vascular resistance in these four patients is markedly lower than that in patients with other forms of secondary pulmonary hypertension, as reported in our study. The mean pulmonary vascular resistance in their case series is 3.13 units, while in our patients it was 14.4 units. It would be difficult to justify the use of such a complicated therapy as long-term prostacyclin infusion in patients with mild pulmonary vascular disease. Certainly, a better understanding of the mechanism of pulmonary vascular disease in the setting of sickle cell disease would aid in the treatment of this serious disorder.

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Cardiac Asystole and Bradycardia as a Manifestation of Left Temporal Lobe Complex Partial Seizure

To the Editor: In the fascinating report by Locatelli and colleagues (1), the authors conjecture a possible association between left temporal lobe epileptic activity and cardiac asystole or bradycardia. The authors cite their own experience with 3 patients, as well as a review of the literature constituting 10 reports on 14



Figure. Polysomnographic recording showing a 10-second cardiac pause during obstructive hypopnea during rapid eye movement (R) sleep. EEG = electroencephalogram; Effort = chest/abdominal respiratory effort; EOG = electrooculogram; EMG = electromyogram; Flow = nasal/oral airflow; LOC = left electrooculogram; ROC = right electrooculogram; SpO₂ = oxyhemoglobin saturation; W = wakefulness.

patients, all of whom underwent simultaneous video electroencephalography–electrocardiography. I would submit, however, that the leap from cortical stimulation studies, in which a cause-and-effect relation may be apparent, to a complex clinical situation with uncontrolled variables is hazardous. Sinus bradycardia and asystole, for example, are also observed relatively frequently in patients with obstructive sleep apnea (**Figure**). In these patients, bradycardia and asystole are considered to be the consequences of airway obstruction and hypoxemia (2). Guilleminault and colleagues (3), for example, observed sinus pauses from 2.5 to 13 seconds in 11% of 400 patients with obstructive sleep apnea. Zwillich and associates (4) observed bradycardia during 95% of apneas; these bradycardiac episodes became more severe as apnea length and oxyhemoglobin desaturation increased.

During a process as complex as a seizure, diverse physiologic effects may be anticipated. Without simultaneous respiratory monitoring to establish the presence of effective gas exchange during the seizure activity, one should be cautious in concluding a cause-and-effect relation between the seizure activity and the observed bradyarrhythmias. This distinction may be of more than academic interest. Locatelli and colleagues describe the use of cardiac pacemakers in the setting of sinus dysfunction or increased vagal tone. As discussed in a recent review (5), cardiac pacing may not be appropriate therapy in the setting of bradyarrhythmias secondary to airway obstruction and hypoxemia because maintaining heart rate increases myocardial oxygen demands at a time of decreased oxygen availability.

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References

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2. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med.* 1977;63:348-58.
3. Guilleminault C, Connolly SJ, Winkle R. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol.* 1983;52:490-4.
4. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Brady-

cardia during sleep apnea. *J Clin Invest* 1982;69:1286-92.

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Pollen Trapped in a Scuba Tank: A Potential Hazard for Allergic Divers

To the Editor: Although available data suggest that patients with asthma have no greater risk for airway obstruction during scuba diving than normal persons (1), we alert atopic patients to a potential hazard associated with the entrapping of submicronic or smaller micronic particles of pollen allergens (2) in scuba tanks. We have verified this risk in a young patient with wide scuba diving experience. The patient had grass-induced hay fever,

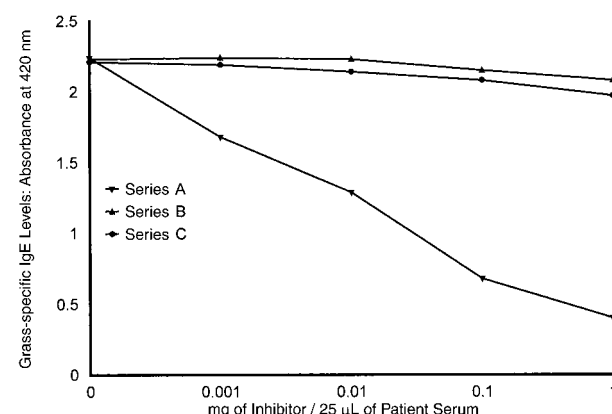


Figure. IgE enzyme allergosorbent test (EAST) inhibition conducted in air extracts from three series of air cylinder testing compared with a grass-coupled allergen disk. Fifty µL of patient serum was added to 100 µL of radioallergosorbent test buffer solution containing lyophilized amounts of extract, in increasing weight, from cylinders in series A (open seaside area during pollen season), series B (open seaside area after pollen season), or series C (closed area), respectively. After 3-hour incubation at room temperature, residual specific (grass) IgE activity was measured by IgE EAST.

and in September 1997 and June 1998 he experienced attacks of dyspnea under water after he had filled his tanks from a certified (DIN 9188) portable breathing air compressor in an open seaside area containing abundant grasses.

Diagnostic findings revealed only borderline methacoline-induced airway hyperresponsiveness with a plateau effect, as is often observed in persons with hay fever (3). A double-blind diagnostic protocol was performed. An in vivo portion involved a bronchial challenge test and skin-prick test, and an in vitro portion involved an IgE enzyme allergosorbent test inhibition procedure (4). This protocol sought to investigate the allergenic activity of the air from three differently charged scuba tanks.

A technician uninvolved in the study charged the tanks in the above-mentioned area during and after pollen season and in a dust- and exhaust-polluted closed area. A skin-prick test and enzyme allergosorbent test were performed with lyophilized extracts (4) of phosphate-buffered saline samples. The samples contained aerosols directly suspended in the phosphate-buffered saline liquid filter and aerosols collected and thawed in a jacketed condenser unit (-20°C) (5). Only the air and air extracts of the tank series conducted during pollen season induced a positive response in the bronchial challenge test or skin-prick test, respectively (Figure on bottom of page 166). The enzyme allergosorbent test inhibition results paralleled those we obtained in vivo and showed that reactivity of reagents in the post-pollen season series was related to grass allergen. We wish to warn atopic patients about this scuba diving-related risk and to recommend that tanks be filled in protected areas during pollen season.

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Correction: Risk for Valvular Heart Disease among Fenfluramine and Dexfenfluramine Users

A few errors appeared in the paper on risk for valvular heart disease in fenfluramine and dexfenfluramine users who had echocardiography before receiving the medication (1).

1. On page 872, the first column in Table 1 under "Diet medication use" should read 48% instead of "47%" for "Fenfluramine-phentermine"; for "Dexfenfluramine," it should read 28% instead of "29%."

2. On page 871, under the heading "Valvular Abnormalities" and subheading "Aortic Valve," the last sentence should read, "Regurgitation was graded as trace (jet area $\leq 2\text{ cm}^2$) . . ." and not "... trace (jet area $\leq 1\text{ cm}^2$) . . ."

3. In the second column of Table 2, 8th row down (page 872), "1" patient was listed as having mild aortic regurgitation that regressed to trace regurgitation. This should read "0" so that the total number of patients in that row adds up to 5.

4. On page 873, in the last paragraph of the result section, for the sentence beginning "Among all patients who took fenfluramine-phentermine . . .," the first risk estimate should be 7.4% (CI, 0.9% to 24.3%) instead of 8.3% (CI, 1.0% to 27.0%). The second risk estimate "after exclusion of those with existing valvular disease . . ." should be 4.5% (CI, 0.1% to 22.9%) instead of 4.0% (CI, 0.2% to 24.9%).

Reference

1. Wee CC, Phillips RS, Aurigemma G, Erban S, Kriegel G, Riley M, et al. Risk for valvular heart disease among users of fenfluramine and dexfenfluramine who underwent echocardiography before use of medication. *Ann Intern Med*. 1998;129:870-4.

Correction: Missing Figure

Because of a printing error, the figure in a recent article on β -blockade after acute myocardial infarction in elderly persons (1) was omitted. The figure is reprinted on this page.

Reference

1. Krumholz HM, Radford MJ, Wang Y, Chen J, Marciniak TA. Early β -blocker therapy for acute myocardial infarction in elderly patients. *Ann Intern Med*. 1999;131:68-54.

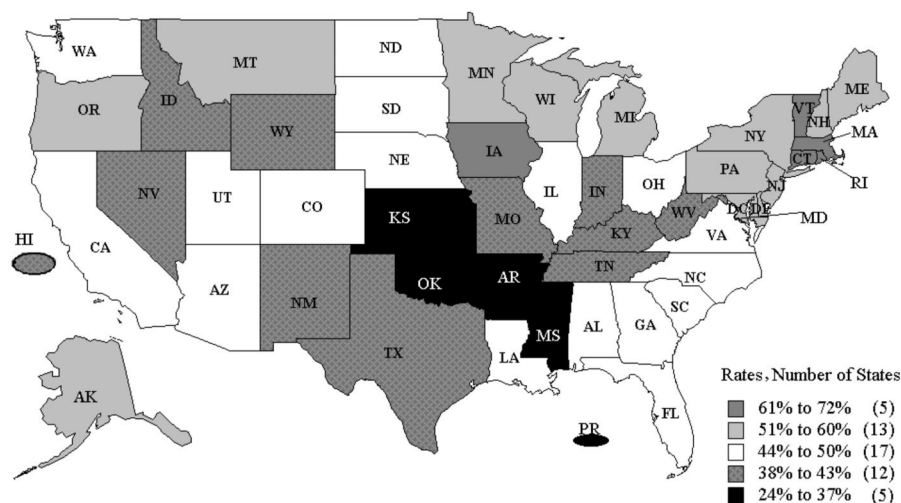


Figure. Use of β -blocker therapy in the United States, by state or territory.