Letters

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should:
• Include no more than 300 words of text, three authors, and five references
• Type with double-spacing
• Send three copies of the letter, a transfer-of-copyright form (see Table of Contents for location) signed by all authors, and a covering letter describing any conflicts of interest related to the contents of the letter
• Provide a self-addressed envelope if they want to be notified that the letter was received

Letters commenting on an Annals article will be considered if they are received within 6 weeks of the time the article was published. Only some of the letters received can be published. Published letters are edited and may be shortened; tables and figures are included only selectively. Authors will be notified if the letter has been received. If the letter is selected for publication, the author will be notified about 3 weeks before the publication date. Unpublished letters cannot be returned.

Therapeutic Theophylline Levels and Adverse Cardiac Events

To the Editor: The recent article by Shannon and colleagues (1) clearly showed the severity of theophylline intoxication. Nearly one quarter of their patients had clinically significant complications when theophylline concentrations were in the toxic range. Of particular interest were patients who developed myocardial infarctions. Adverse cardiovascular effects can occur even when serum theophylline concentrations are in the therapeutic range. We followed a 61-year-old white woman who experienced an unusual combination of complications during treatment with intravenous aminophylline and nebulized albuterol. She had no history of heart disease except for left ventricular hypertrophy confirmed by echocardiography. A dynamic left ventricular outflow tract obstruction developed, which led to a myocardial infarction. Her serum theophylline level was 11.2 mg/L. Cardiac catheterization showed no fixed coronary artery stenoses. Hemodynamic changes resolved after discontinuation of aminophylline therapy. Bittar and colleagues (2) previously showed that aminophylline can cause tachycardia and myocardial ischemia, even at recommended doses. Aminophylline is a positive inotrope and has been reported to induce dynamic left ventricular outflow obstruction (3). Moreover, it antagonizes the vasodilatory effect of adenosine on coronary arteries (4). All these mechanisms can provoke myocardial ischemia and, as in our patient, myocardial infarction.

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References

In response: We appreciate Dr. Raggi's comments on the potential for normally therapeutic theophylline levels to produce significant cardiac disturbances. This risk has been reported by many investigators. In a separate study, Bittar and colleagues (1) reported that among elderly patients receiving theophylline, those with serum concentrations between 10 and 20 mg/L had an 3.7-fold greater risk for cardiac disturbances than did patients of similar age with nondetectable serum theophylline concentrations. In an in vitro study, Lin and coworkers (2) found that theophylline has specific arrhythmogenic effects on human atrial tissue. Although their data suggest that theophylline has direct actions on cardiac membrane depolarization, other theories of theophylline-induced cardio toxicity include the drug's ability to antagonize the cardioprotective effects of endogenous adenosine (for example, coronary artery dilation) as well as its ability to stimulate plasma catecholamine activity and to increase myocardial oxygen demand. These findings provide consistent evidence that adverse cardiac events may occur not only in patients with theophylline intoxication (3) but also in patients whose levels are within the therapeutic range.

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Is Preventing Sudden Cardiac Death Realistic?

To the Editor: The recent overview of sudden cardiac death by Myerburg and colleagues (1) was informative. However, as a general internist, I have difficulty applying this knowledge preventively. The pathophysiology of sudden cardiac death is multifactorial and complex. To be effective, prevention must be targeted at the general population.

The worst outcome among survivors of a major cardiovascular event is seen in the subgroup with low ejection fractions (<30%). Because the underlying cause in most of these patients is coronary artery disease, does ultrasonic computed tomography play a role in identifying coronary calcifications in the screening of these patients?

In view of the unexpected results of the Cardiac Arrhythmia Suppression Trial (CAST) (2), would a different outcome in the treated group have resulted from the use of oral magnesium supplements (4)?

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References

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In response: We appreciate Dr. Sanchez's comments and fully agree that for the general internist practicing in 1994, little can be done to identify risk among persons with no evidence of underlying disease, other than doing standard preventive techniques aimed at decreasing the development of coronary artery disease. After the disease has developed, specific markers are available for at least some of the risk factors associated with sudden death. Multiple strategies will probably be necessary, depending on the size and risk of the targeted population base. The hope for the future is the evolution of simple screening techniques, which could allow the identification of high-risk clusters hidden within larger populations. For example, a currently useful clinical technique for identifying a high-risk subgroup in a general population is the response of the QT interval on the standard 12-lead electrocardiogram to class I-A antiarrhythmic drugs such as quinidine. Patients with idiopathic exaggerated QT prolongation appear to be at an increased risk for potentially fatal torsade de pointes (1). This example is of limited importance because it occurs infrequently.

Recent observations of specific T-wave changes in response to ischemia and reperfusion (2) may soon provide a marker identifying larger patient clusters at risk for fatal arrhythmias during ischemic events. Experimental studies suggest that subgroups may have specific ion channel patterns controlling the response to ischemia and reperfusion. These patterns may predispose to such T-wave changes and to fatal arrhythmias (3).

In regard to general screening, the use of ultrafast computed tomography is problematic. The technique appears to provide a noninvasive means of identifying patients with emerging structural disease of the coronary arteries (4), but it is not yet useful for screening for risk for sudden cardiac death in the general population. In our analysis of the role of dynamic risk factors clusters hidden within larger populations. For example, a currently useful clinical technique for identifying a high-risk subgroup in a general population is the response of the QT interval on the standard 12-lead electrocardiogram to class I-A antiarrhythmic drugs such as quinidine. Patients with idiopathic exaggerated QT prolongation appear to be at an increased risk for potentially fatal torsade de pointes (1). This example is of limited importance because it occurs infrequently.

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In response to the question about the CAST study, no data from CAST suggest that a serum magnesium abnormality contributed to outcome, and we believe that, based on existing knowledge, the routine use of magnesium supplementation to prevent sudden cardiac death (or malignant ventricular arrhythmias) is not warranted for the general population.

References

Phenytoin and Ranitidine Interaction

To the Editor: We report a rare case of elevated phenytoin plasma concentration associated with the concurrent use of ranitidine that persisted for several days after therapy with phenytoin was discontinued but that declined rapidly after ranitidine was withdrawn.

A 77-year-old African-American man with a 1-year history of severe stroke and residual right hemiparesis had entered our hospice for a new-onset seizure 4 weeks before this hospitalization. He was treated with phenytoin, 100 mg orally three times daily, and was discharged 1 week later with oral phenytoin suspension, 300 mg three times daily. Ranitidine, 150 mg orally twice daily, was added 5 days later. The patient returned because of abdominal pain; a plasma phenytoin level done the morning after his admission was 43 μg/mL (normal, 10 to 20 μg/mL). Therapy with phenytoin was discontinued, but plasma concentrations remained high after 1 week (Table 1).

The patient's other medications included acetaminophen and codeine elixir (12.5 mL orally every 4 hours as necessary) and acetaminophen suppositories (650 mg rectally every 4 hours as necessary). The patient had a normal serum creatinine level of 1.2 mg/dL (normal, 0.5 to 1.4 mg/dL) but a low serum albumin of 36 g/L (normal, 35 to 52 g/L). Because we suspected that therapy with ranitidine might be inhibiting the metabolism of phenytoin, it was discontinued on day 8. The plasma phenytoin concentration then declined.

Table 1. Phenytoin Concentrations during Ranitidine Use*

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Phenytoin Concentration (μg/mL)</th>
<th>Decrease in Phenytoin Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43.0</td>
<td>Phenytoin therapy discontinued</td>
</tr>
<tr>
<td>2</td>
<td>45.8</td>
<td>2.8 (6.5)</td>
</tr>
<tr>
<td>3</td>
<td>39.2</td>
<td>-6.6 (14.4)</td>
</tr>
<tr>
<td>4</td>
<td>26.9</td>
<td>-9.3 (23.7)</td>
</tr>
<tr>
<td>5</td>
<td>29.6</td>
<td>-0.3 (1.0)</td>
</tr>
<tr>
<td>6</td>
<td>27.6</td>
<td>-2.0 (6.7)</td>
</tr>
<tr>
<td>7</td>
<td>26.0</td>
<td>-1.6 (5.8)</td>
</tr>
<tr>
<td>8</td>
<td>NA</td>
<td>Ranitidine therapy discontinued</td>
</tr>
<tr>
<td>9</td>
<td>18.3</td>
<td>-7.7 (29.6)</td>
</tr>
<tr>
<td>10</td>
<td>14.7</td>
<td>-3.6 (19.7)</td>
</tr>
<tr>
<td>11</td>
<td>10.1</td>
<td>-4.6 (31.3)</td>
</tr>
<tr>
<td>12</td>
<td>NA</td>
<td>Oral phenytoin restarted, 100 mg every 8 h</td>
</tr>
</tbody>
</table>

* Rate of phenytoin concentration decrease (measured approximately every 24 h) slowed toward hospital days 5 to 7 and increased during hospital days 9 to 11 (after discontinuation of therapy with ranitidine). NA = not applicable.
Sun Exposure and Amyotrophic Lateral Sclerosis

To the Editor: Recently, mutations in the gene for Cu/Zn superoxide dismutase, an enzyme that scavenges the toxic free-radical superoxide anion \( (O_2^-) \), were reported in patients with familial amyotrophic lateral sclerosis (1). This defective dismutase could be responsible for progressive motor neuron damage in amyotrophic lateral sclerosis. Although the familial version of the disorder has several unique features distinguishing it from the sporadic disease, the clinical and pathologic similarities (2) suggest a common pathogenesis. If free radicals play a role in the sporadic disease, one would expect a higher disease incidence in populations exposed to environmental factors, such as solar energy, associated with increased production of \( O_2^- \) (3).

We therefore examined the records of the Hadassah University Hospital and identified 69 hospitalized patients who developed sporadic amyotrophic lateral sclerosis between 1979 and 1992. From 1979 to 1985, 31 patients developed the disease, and 38 developed it during the next 7 years. The patients included 50 men (72.4%) and 19 women (mean age at onset, 54 years) and 19 women (mean age at onset, 57 years). Mean age at onset for the entire group was 54.3 years. These sex and age distributions are in accord with other studies (2), including data on patients with the disease in Israel (4). Twenty-seven patients (39%), all men, were either farmers or building construction workers. This observation was remarkable because the percentage of people who work in agriculture and building construction in Israel was no more than 12% between 1980 and 1990 (5).

The interpretation of this observation requires caution because we were unable to obtain information on length of exposure to solar energy and because ours is a referral hospital and therefore represents a highly selected patient population. In addition, we did not have an appropriate control group.

Nevertheless, our findings indicate the possibility of an increased incidence of sporadic amyotrophic lateral sclerosis among persons chronically exposed to sunlight. If this is true, we suggest the following hypothesis: The disease, both sporadic and familial, results from free-radical-induced motor neuron cellular damage. In the familial disease, a partially functional, mutated superoxide dismutase fails to protect from \( O_2^- \)-induced damage during many decades of incompletely effective scavenging. In some sporadic cases, the motor neuron damage is caused by the increased load of free radicals in the presence of environmental factors that produce them in excess.

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References

A Conflict of Interest "Revisited": The Use of Stereotypes

To the Editor: You published a fictional essay (1) about lawyers, physicians, patients, and families who struggle to solve their problems. Named characters include attorneys Slattery and Prudhomme, Dr. Simpson, Allen Heath, Jennie Heath, and Mrs. Heath. Then there is attorney Isadore Lavinsky, described as "scum, a street fighter . . . He'll do anything . . . perjury, bribery, witness tampering . . ." The only identifiable Eastern European Jew is the scummy lawyer, Igge Lavinsky.

Why give the Jewish name to the unsavory, unethical attorney? Everyone else gets a neutral “American” name. What is the message? Do the author and the editors really mean to associate Jews with the unethical, tricky, and underhanded? Is this connection made through malice, ignorance, or merely insensitivity? Is stereotypical writing now to be expected in future issues of Annals? Your editorial judgment in publishing this piece is suspect and disappointing.

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Reference

To the Editor: I asked a dozen colleagues what they thought might be the background of lawyer Igge Lavinsky (1), carefully using only the words of the narrator in the story when I described this man: "scum, a street fighter . . . He'll do anything . . . perjury, bribery . . . anything." Not surprisingly, no one thought the unscrupulous Lavinsky might have been a family of Mongolian horsemen, Australian aborigines, Viking sailors, or Bedouin shepherds or that Igge was short for Ignatius with Catholic roots in some Eastern European country. "Why, he's supposed to be Jewish; what else could he be?!" was everyone's response. The ancient, malicious stereotype of the shyster Jew was immediately recognized.

LaCombe is a skilled, accomplished writer, and, judging from his writing, he is an erudite, sensitive person. I regretfully assume that his story is based on a real-life experience. The moral and ethical issues it illustrates deserve contemplation. But did poor Mrs. Heath's salvation have to depend on such a blatant caricature of a Jew? LaCombe seems to have given the lawyers' names considerable thought, starting with clean Prudhomme, descending midway to Slattery, and literally hitting the floor with Igge. Would the story have been less effective if the character Igge had been named Ed Lavin or, for that matter, Jean Coutemarsh, Thomas O'Connor, J. P. Brown, Jr., or Ismail Ibn Said?

Even if this association was unintended, I think many Jewish readers will see in LaCombe's story a pointless, insensitive resurrection of an offensive racial stereotype. I am surprised at LaCombe and the Editors of Annals.

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Reference
of freedom of speech by amateur author physicians? Would Dr. LaCombe have countenanced a similar jibe at his own ancestors or coreligionists? Or did the editor of this rubric "On Being a Doctor" simply lack sensitivity to the obvious anti-Jewish slur?

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Reference

In response: My apologies to my Jewish colleagues.

When I wrote "A Conflict of Interest," which was based on real-life experience, I retained both the character and ethnicity of Iggie Lavinsky. It never occurred to me that I was creating an offensive stereotype.

When the story was performed at Mayo Clinic, one Jewish couple raised these same objections to me, and I was both surprised and mortified. I checked with the performers, all Jewish. None had had a problem with Lavinsky. But such judgments are in the eye of the beholder, and I can understand Dr. Klein's sensitivity.

Later, I offered the story to Annals, raising the issue of Lavinsky to the Editors as well. The Editors felt a more "neutral" name for the Lavinsky character would be advisable but left the final decision to me. The readers' instant recognition of the ruthless lawyer's name. A bland name would never do. I might have used Augie Donatelli or Mickie Joe Doherty—but that seemed to me less honest than staying close to reality. And so Iggie Lavinsky lived on.

Now back to the "eye of the beholder" point. In the story, Mrs. Heath has Prudhomme's firm initially represent her. Reading between the lines, it would seem they will lose the case through their own ineptitude, and Mrs. Heath will be "forgotten, with barely an apology. She and her four children . . . would be the ultimate victims." Prudhomme is not a neutral name, Dr. Zucker; nor is it terribly "clean" in this case, Dr. Sobel. Please note, Dr. Klein, that it is French-Canadian; I have yet to hear from my compatriots on this one.

Finally, let us look back at the story from our earned perspectives: Is the narrator's attorney truthful in his rendition of events at the story's beginning? How is the law best served in this story? Which attorney in the story best serves his client? Perhaps this, by a Jewish attorney in response to his reading "Conflict" can help us here: "It all goes to show that life is not simple and even the Lavinskys of the world can, on occasion, help the needy. Life would be much simpler if the only colors were black and white. It's those darn grays that cause confusion . . . the search for truth and meaning is an exciting endeavor. . . ."

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The Editors apologize to readers who saw Dr. LaCombe's piece as ethnic stereotyping. Its publication should not be taken as reflecting any editorial policy, and the Editors regret any offense it gave.

Correction: Questions Patients Should Ask about Laparoscopic Cholecystectomy

To the Editor: Two sentences in a recently published letter (1) conveyed meanings other than those intended. In the sentence, "Ransohoff and Gracie appropriately advise caution in interpreting the published series, given the small number of open cholecystectomies," the word "open" should be replaced by "laparoscopic."

In the fifth paragraph, the Island Peer Review Organization hotline described was not uniquely established for inquiries from beneficiaries regarding laparoscopic cholecystectomy but for inquiries on various medical care issues, including laparoscopic cholecystectomy. Thus, the sentence "To assist patients in assessing the experience and competency of their potential laparoscopic surgeon, in 1992 we instituted a toll-free hotline on laparoscopic cholecystectomy for Medicare and Medicaid beneficiaries," should read "To assist patients with medical care issues, in 1992 we instituted a toll-free hotline for Medicare and Medicaid beneficiaries."

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Reference