Sequelae and Serologic Outcome in Persons with Hepatitis B Virus Infection

TO THE EDITOR: The study by McMahon and colleagues on hepatitis B virus (HBV) infection in Alaska natives (1) suffers from a major limitation: The authors failed to search for HBV DNA in serum. This makes it impossible to judge whether the natural history of the disease is indeed benign. Contrary to old assumptions, it has become clear that seroconversion to hepatitis B e antigen antibody (anti-HBe) does not necessarily indicate cessation of viral replication and a more benign disease course. Instead, it indicates persistence of HBV replication in a substantial proportion of patients. Such persistence is sometimes (2) but not always (3) related to prevalence of mutant viral populations. Patients who are positive for anti-HBe can be subdivided into two groups: those without viral replication (no HBV DNA or very low levels on polymerase chain reaction) and with no progression of liver damage, and those with ongoing viral replication (fairly high levels of HBV DNA) and progressive liver damage. The latter are at considerable risk for cirrhosis and hepatocellular carcinoma (4).

Successful antiviral therapy does not merely accelerate clearance of hepatitis B e antigen (HBeAg) but also seems to reduce the chances that anti-HBe is related to prevalence of mutant HBV (5). We believe any studies of the natural history of HBV infection should aim at defining the percentage of patients with continuous viral replication after stable seroconversion from HBeAg to anti-HBe. Studies on this important point are essential to determine whether the duration of HBeAg positivity before anti-HBe seroconversion can influence the subsequent disease course (that is, whether early or late seroconversion affects persistence of HBV replication). It would then be possible to propose antiviral treatment to a more restricted HBeAg-positive patient population, given the high costs and not very successful outcome of interferon or lamivudine treatment.

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References

IN RESPONSE: Drs. Cainelli and Vento correctly point out that information regarding HBV DNA levels in HBeAg-positive persons would be important in understanding the natural history of HBV. Knowledge of HBV genotype, presence or absence of precore variant, and liver aminotransferase levels could also be helpful in selecting patients for treatment (1, 2). When our study began in 1982, HBV DNA levels were not readily obtainable. In addition, HBV DNA levels alone are not sufficient to determine whether progressive liver damage is present. Aminotransferase levels, the more important indicator, along with HBV DNA levels above 100 000 copies/mL, correlate with ongoing clinical hepatitis on biopsy (3).

We were unable to determine aminotransferase levels in our patients because before 2000 most villages did not have centrifuges, and aminotransferase levels are not stable unless blood specimens are separated immediately. A recent practice guideline from the American Association for the Study of Liver Diseases does not recommend that HBV DNA levels be obtained in persons with inactive HBV (those who are positive for anti-HBe but have normal aminotransferase levels) (4). In 1992, we tested alanine aminotransferase levels within 36 hours of sampling in 192 carriers, 115 males and 77 females, who were from 17 villages and were between 10 and 70 years of age. Levels were normal in 131 of 162 anti-HBe–positive carriers (80.9%) but elevated in 18 of 30 of HBeAg–positive carriers (60%) (P > 0.01). This finding suggests that most Alaska natives with chronic HBV infection who seroconvert from HBeAg to anti-HBe do not have active hepatitis.

We have embarked on a 4-year prospective study to examine HBV DNA levels, genotypes, and precore mutants in persons in our population with chronic HBV infection. We hope that information gained from this study will address the important issue that Drs. Cainelli and Vento have raised, namely identifying which carriers could be targeted for antiviral therapy.

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References
Risk Index for Postoperative Pneumonia

TO THE EDITOR: Although we laud the intent and scope of Arozullah and colleagues’ study on predicting postoperative pneumonia after major noncardiac surgery (1), we note that analysis of intraoperative factors was limited to type of anesthesia. Inquiring only whether patients have received general or regional anesthesia, however, cannot readily summarize the complex nature of state-of-the-art anesthesia care. As perioperative physicians involved in the management of patients before, during, and after surgery, we suggest that the risk index proposed by Arozullah and colleagues may be incomplete without greater attention to perioperative factors.

For example, although the authors identify preoperative blood transfusion as an important predictor of postoperative pneumonia, no mention is made of intraoperative blood loss or fluid administration, which can alter the incidence of postoperative respiratory complications (2). In addition, postoperative pain management strategies were not discussed. In a similar patient sample, use of epidural analgesia for aortic surgery (3) improved outcomes. Moreover, Arozullah and colleagues did not examine the adequacy of preoperative evaluation. Were potentially modifiable risk factors, such as malnutrition, respiratory infection, or symptomatic obstructive lung disease, adequately addressed in all patients preoperatively? Although these issues may seem mundane, perianesthetic outcomes can depend on close attention to such detail.

Anesthetic management of patients undergoing major noncardiac surgery has evolved dramatically in the 5 years since Arozullah and colleagues’ study began. Increased use of epidural analgesia (used in <3% of their study sample) and β-blockers in patients at risk for cardiac disease (4) are two recent modifications in anesthetic care that may have affected their results. We congratulate Arozullah and colleagues on performing an important study and hope that subsequent work will focus on perioperative as well as preoperative risk factors.

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References

IN RESPONSE: There are two distinct yet related goals during preoperative evaluation. The first is to accurately predict the risk for postoperative complications, and the second is to modify risk factors to reduce the risk for complications. The main purpose of our study was to contribute to accomplishing the first goal by developing and validating a risk index for predicting postoperative pneumonia using information that is readily available to clinicians before surgery. We purposely did not include potential risk factors, such as intraoperative blood loss or postoperative pain management, because this information is not typically available before surgery and is therefore not useful for preoperative risk assessment. A risk index should not be considered “incomplete” simply because it does not include all possible risk factors. Rather, the value of a risk index should be judged based on its ability to accurately predict the outcome it was designed to predict.

Excluding intraoperative and postoperative risk factors limits the risk index’s contribution to accomplishing the second goal of modifying risk. Risk reduction is usually accomplished through interventions proven useful in randomized, controlled trials. However, the ability to accurately select high-risk patients usually precedes the development of useful interventions because most interventions are targeted to high-risk patients. For example, preoperative cardiac risk indexes were used for more than 20 years before the usefulness of perioperative β-blockers for high-risk cardiac patients was proven (1). It is our sincere hope that the postoperative pneumonia risk index will serve as a similar foundation for future patient-level and hospital-level interventional studies aimed at reducing the incidence of postoperative pulmonary complications.

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Extended Out-of-Hospital Low-Molecular-Weight Heparin for Prophylaxis against Deep Venous Thrombosis

TO THE EDITOR: The meta-analysis by Hull and colleagues (1) on extended out-of-hospital low-molecular-weight-heparin (LMWH) for postoperative prophylaxis against deep venous thrombosis (DVT) is provocative, and important questions should be raised about its recommendations. The safety of extended prophylaxis remains uncertain.

Hull and colleagues found a low rate of bleeding complications. However, the patients involved had been screened and were followed under study circumstances. The patients who are at highest risk for postoperative DVT are usually those who are most frail and have comorbid conditions that increase risk for bleeding. Many patients also have reduced renal clearance of LMWH because of overt renal disease or advanced age.

In the studies included by Hull and colleagues, LMWH therapy was continued for 27 to 35 days. This duration is similar to that...
required for unfractionated heparin to substantially reduce bone density and symptomatic vertebral fracture in 30% and 2% to 3% of patients, respectively (2, 3). Low-molecular-weight heparin has been shown to cause fewer vertebral fractures in 3 to 6 months than does unfractionated heparin. Reduction in bone formation was demonstrated clearly in rats treated with 32 days of LMWH (4). Data evaluating bone density after 1 month of LMWH use are insufficient (3).

The patients in Hull and colleagues’ analysis were discharged between day 6 and 14 of LMWH prophylaxis (5). Heparin-induced thrombocytopenia typically occurs between 5 and 10 days of LMWH use. Although the risk is probably lower with LMWH than with unfractionated heparin, this complication would manifest after hospital discharge, diagnosis would be delayed, and continued therapy would be potentially devastating (3).

It is premature to conclude that extended prophylaxis should be continued in real-world situations. We agree that some patients may benefit from this approach but maintain that it cannot yet be recommended for all patients.

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**Roslyn F. Schneider, MD**
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**References**

**IN RESPONSE:** Drs. Murashige and Schneider overstate the issue when they question the safety of extended prophylaxis, particularly in the context of patients receiving out-of-hospital LMWH after elective hip surgery. In our meta-analysis and in another study (1), we found that many randomized trials convincingly demonstrated safety in terms of an absence of major bleeding (0 of 1091 patients). The frequencies of minor bleeding (2.7%) and complicated wound hematoma (0.5%) were low and were similar to those observed in the placebo groups (1).

Drs. Murashige and Schneider raise important issues about renal function, osteoporosis and associated vertebral fracture, and thrombocytopenia. These issues are gradually becoming better understood in terms of LMWH administration. Persons undergoing elective hip surgery are by definition voluntary patients and therefore are more robust and healthier than patients undergoing urgent surgery for a fractured hip. Increasing evidence shows that a single high-risk dose of LMWH (which is much less than a treatment dose) is safe in elderly patients without markedly elevated serum creatinine concentrations. Indeed, the evidence suggests that dose adjustment is not necessary unless the creatinine clearance falls below 0.33 mL/s (20 mL/h) (2). Clinically evident osteoporosis is more common in persons receiving unfractionated heparin than in those receiving LMWH (3). Furthermore, the duration of LMWH prophylaxis is short (35 days) compared with the many months of use in pregnant patients receiving therapeutic doses, in whom osteoporosis has been rare. Thrombocytopenia is less frequent in patients taking LMWH than in those taking unfractionated heparin (1 to 2 cases in 1000 patients vs. 2 to 3 cases in 100 patients). Nevertheless, monitoring of platelet count is warranted in the first 2 weeks of prophylaxis.

Our conclusion that extended out-of-hospital prophylaxis with LMWH should be considered in patients undergoing elective hip arthroplasty is valid based on evidence of effectiveness and safety. We agree that clinical judgment is also a crucial issue in deciding which patients should receive extended out-of-hospital prophylaxis.

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**Quality Indicators for Management of Osteoporosis**

**TO THE EDITOR:** We disagree strongly with Quality Indicator 9 in the article by Grossman and MacLean on management of osteoporosis in vulnerable elders (1). This indicator states that male vulnerable elders who have osteoporosis and are hypogonadal should be offered testosterone treatment because it “has been shown to improve bone density and therefore may decrease fracture risk” (1). Hypogonadal men are defined as those with low testosterone levels. This conclusion infers that low testosterone levels in men are causally related to osteoporosis, that testosterone treatment is safe and effective, and that other available treatments are less effective or unsafe. Current evidence does not support these assumptions.

Low testosterone levels, particularly free testosterone levels, are common in older men but are not invariably associated with osteoporosis (2). It is not certain what role this age-related decline in testosterone levels plays in causing osteoporosis. In fact, recent studies suggest that testosterone levels are only weakly related to bone mass in older men and that endogenous estrogen levels influence...
bone mass to a greater extent (3). Of importance, no randomized trials have examined the ability of testosterone therapy to prevent fractures among men with osteoporosis and low testosterone levels, and trials with bone density end points are inadequate to assess fracture prevention (4). Of great concern is the paucity of long-term data on the safety of testosterone treatment; concerns about cardiovascular disease and prostate cancer have been raised (4). Furthermore, safe and effective alternative treatments for men with osteoporosis, with and without low testosterone levels, have been tested in large placebo-controlled trials (5). Until well-done clinical trials demonstrate that testosterone treatment prevents fractures in men without causing potentially serious side effects, we believe that such therapy should be reserved for men with symptomatic hypogonadism and that most men with osteoporosis should be treated with a bisphosphonate.

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References

Automated External Defibrillators

TO THE EDITOR: Takata and colleagues (1) do a nice job of reviewing the recent advances that have led to the expanding use of automated external defibrillators (AEDs). However, although AEDs clearly save lives, greater attention must be devoted to understanding their cost-effectiveness. One study referenced by Takata and colleagues (2) instructive and reassuring. In reviewing the bibliographies, however, I noted that there was no mention of a study by Dalen (3). Craven reasoned that aspirin in high doses might provide similar anticoagulant efficacy. Dalen reported that by 1956, Craven’s series included approximately 8000 men. He had gradually tapered the dose of aspirin and ultimately concluded that “one aspirin per day would probably suffice therapeutically.”

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Note: The opinions in this article are those of the authors and do not represent official policy of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

References
2. Nichol G, Hallstrom AP, Ornato JP, Riegel B, Stiell IG, Valenzuela T, et al. Potential cost-effectiveness of public access defibrillation supported by the U.S. National Heart, Lung, and Blood Institute, which is examining the life-saving potential and cost-effectiveness of AEDs. This trial will be completed next year.

Aspirin for the Primary Prevention of Cardiovascular Events

TO THE EDITOR: I found the recommendations of the U.S. Preventive Services Task Force (1) on aspirin for the primary prevention of cardiovascular events and the accompanying meta-analysis by Halden and colleagues (2) instructive and reassuring. In reviewing the bibliographies, however, I noted that there was no mention of a remarkable but obviously unappreciated contribution provided almost 50 years ago by Lawrence L. Craven. James E. Dalen, MD, Editor of Archives of Internal Medicine (3), discussed this contribution in a 1991 editorial.

According to Dalen, Craven was a general practitioner in Glendale, California. In 1950 (at age 67), he reported the first of three clinical studies involving the use of aspirin as prophylaxis against coronary (and subsequently cerebrovascular) thrombosis (4–6). At that time, patients with acute myocardial infarction were being treated with warfarin anticoagulants; Craven reasoned that aspirin in high doses might provide similar anticoagulant efficacy. Dalen reported that by 1956, Craven’s series included approximately 8000 men. He had gradually tapered the dose of aspirin and ultimately concluded that “one aspirin per day would probably suffice therapeutically.”

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Dalen noted that Craven’s studies were uncontrolled, and he mused that “as a medical editor, I wonder if I would have accepted
[his] 1950 letter to the editor for publication” (3). Like those of most prophets, Craven’s recommendations went unheeded, but his prescience and his investigative efforts deserve historical note.

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References

Caring for Patients at the End of Life

TO THE EDITOR: Dr. Parker (1) is to be applauded for bringing up end-of-life issues in a medical journal. I was disturbed, however, by his statement that one patient’s “Catholic beliefs forbade her to refuse life-sustaining treatment.” Since there is so much anti-Catholic bigotry today, it is important to correct misrepresentations of Catholic teaching regardless of the motivations of the author (which I assume to be noble). Catholicism does not forbid or command patients to refuse treatments in the context described by Dr. Parker. It does forbid health care workers to purposely or artificially hasten a natural death.

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Reference

The Other Résumé

TO THE EDITOR: I squirmed as I read Dr. Cotton’s provocative article, “The Other Résumé” (1). The author’s reflections on his professional and personal success mirror disturbing, often unspoken prevailing values. Balancing professional and family life will always be challenging. Physicians need to make sacrifices in order to take the best possible care of patients and to advance science. Families need to understand that our schedules are unpredictable but also deserve our active participation in family life.

The issue of Annals containing Dr. Cotton’s article arrived as I was carving jack-o’-lanterns and jumping in the autumn leaves with my daughter. Of course, I might have spent the day working in the laboratory, polishing up a manuscript, or skimming the latest journals. These tasks have their own rewards but compete with family for a limited supply of nights and weekends.

Dr. Cotton’s assertion that his record is not what he might wish is troubling. Each of us has a different niche to fill. Dr. Cotton has seminary training, and medicine is often a pastoral exercise; perhaps he has special gifts in this area. He may never have the chance to address a national meeting of scholars, and Cotton may never be a household name like Folkman, Crichton, or Sacks. But when did taking compassionate, excellent care of patients become something to be ashamed of?

Dr. Cotton claims that students appreciate his teaching. Teaching ability and clinical acumen are more difficult to measure than grants and publications, but they are not worthless. In many academic medical centers, physicians without extramural research funding are still considered second-class citizens. Although this perception is changing, it seems to have rubbed off on Dr. Cotton. In any case, with the publication of his manuscript in Annals, Dr. Cotton now has an article in a front-rank journal to put on his professional résumé. Certainly this should give him some satisfaction.

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Reference

It’s Only 50 Cents

TO THE EDITOR: I was moved by Daniel C.R. Chen’s essay, “It’s Only 50 Cents” (1), and plan to use it to teach medical students about the many ways in which they can care for patients and relieve suffering with very little medical knowledge. I am struck, however, by Dr. Chen’s statement that when the patient he wrote about cried, “We [the physicians] didn’t know how to respond. It was a humanizing moment and we cried with him, although not openly.”

Why are physicians so reluctant (afraid?) to cry openly? Crying, after all, is an honest (and clearly human) response to another person’s pain, suffering, and loss. I have found that a majority of medical students do cry out of compassion (2). It is time to admit that physicians can and should express honest emotion and to do away with the need for the parenthetical phrase “although not openly.”

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References
Rapid Development of Massive Tendon Xanthomas following Highly Active Antiretroviral Therapy

TO THE EDITOR: Hyperlipidemia, lipodystrophy, insulin resistance, and hyperglycemia are well-described side effects of HIV treatment with highly active antiretroviral therapy (HAART) (1–3). Although substantial increases in triglyceride and cholesterol levels have been associated with HAART, there have been no reports to date of xanthomas developing after treatment with these drugs (4, 5). We describe one of the first cases of rapidly developing massive xanthomas of the tendons in a 41-year-old HIV-positive man.

In our patient, lesions were first noted approximately 12 months after HAART (stavudine, 80 mg/d; lamivudine, 300 mg/d; saquinavir, 2400 mg/d; and ritonavir, 1200 mg/d) was started; they progressed rapidly over the next 18 months. The patient had a history of combined dyslipidemia (total cholesterol level, 7.5 mmol/L [290 mg/dL]; triglyceride level, 3.1 mmol/L [274 mg/dL]) that predated treatment for HIV infection. On physical examination, large tendon xanthomas were noted over the metacarpophalangeal and metatarsophalangeal joints, elbows, and patellae (Figure). The Achilles tendons were markedly thickened. Two small periocular xanthelasmas were noted. Biopsy of a lesion showed a xanthomatous reaction, with spindle and foamy cells staining strongly positive for the macrophage marker CD68 and the fibrohistiocytic cell marker factor XIIIa.

The patient’s fasting plasma lipid profile during combination lipid-lowering therapy (pravastatin, 20 mg/d, and micronized fenofibrate, 200 mg/d) was as follows: total cholesterol level, 11.92 mmol/L (460 mg/dL); triglyceride level, 9.31 mmol/L (824 mg/dL); high-density lipoprotein cholesterol level, 0.82 mmol/L (32 mg/dL); low-density lipoprotein cholesterol level, 5.08 mmol/L (196 mg/dL); very-low-density lipoprotein–triglyceride level, 7.45 mmol/L (659 mg/dL); very-low-density lipoprotein cholesterol level, 4.73 mmol/L (183 mg/dL); intermediate-density lipoprotein cholesterol level, 0.49 mmol/L (19 mg/dL); total apolipoprotein B level, 1.5 g/L; and very-low-density lipoprotein–apolipoprotein B level, 52.8 g/L. Particles of low-density lipoprotein were small (peak diameter, 24.1 nm). Apolipoprotein E phenotype and genotype were E3/E3 and e3/e3, respectively. Genetic analysis did not reveal mutations of the low-density lipoprotein receptor gene, apolipoprotein E gene, or apolipoprotein B gene.

In this patient, we speculate that HAART-induced aggravation of an underlying lipid disorder caused massive accumulation of cholesterol in the tendons over a short period.

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References
Pneumonitis Associated with Nonsteroidal Antiandrogens: Presumptive Evidence of a Class Effect

TO THE EDITOR: Hypersensitivity pneumonitis, a serious pulmonary disease that is caused by many drugs, is associated with mortality rates of less than 1% (1, 2). Nilutamide, a nonsteroidal antiandrogen used for prostate cancer treatment, is a common cause of hypersensitivity pneumonitis, with reported rates of 1% to 2% (2). For all drugs, diligent postmarketing surveillance is required to ensure drug safety. To date, one case of pneumonitis with bicalutamide and one with flutamide have been reported (3, 4).

We reviewed all cases of pneumonitis associated with bicalutamide, flutamide, and nilutamide reported in MedWatch, the U.S. Food and Drug Administration’s passive reporting database, between 1998 and 2000. The case definition included dyspnea, new pulmonary infiltrates, no evidence of infection, and one or more of the following: improvement with drug discontinuation, recurrence of findings with rechallenge, or biopsy evidence of pneumonitis. The incidence was estimated by using the following equation: number of pneumonitis cases/number of persons using nonsteroidal antiandrogens. Numbers of persons using nonsteroidal antiandrogens were obtained from IMS, Philadelphia, Pennsylvania.

Pneumonitis occurred in 12 patients receiving bicalutamide, 16 patients receiving flutamide, and 50 patients receiving nilutamide at a median of 7.5, 5, and 8 weeks of treatment, respectively (Table). Two patients with bicalutamide-associated pneumonitis and one with flutamide-associated pneumonitis concomitantly developed hepatitis, and 1 patient with nilutamide-associated pneumonitis developed vision changes. Rechallenges led to recurrences in 6 patients, 2 of whom were rechallenged with a different nonsteroidal antiandrogen. Three bicalutamide-treated patients, 7 flutamide-treated patients, and 4 nilutamide-treated patients died, including 1 patient who had two episodes of bicalutamide-associated pneumonitis. Survivors had shorter treatment periods than those who did not survive (median, 3.5 weeks vs. 8 weeks; P < 0.01) and were more likely to have received antiandrogen monotherapy (35.7% vs. 3.2%; P < 0.01). An estimated 0.77% of the 6480 nilutamide-treated patients, 0.04% of the 41 700 flutamide-treated patients, and 0.01% of the 86 800 bicalutamide-treated patients developed pneumonitis during the study period.

Physicians should be aware that pneumonitis is a class effect that can occur with antiandrogens, although its incidence is lower with flutamide and bicalutamide.

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Disclosure: Dr. Bennett has been a consultant to Cell Pathways, Schering-Plough, Inc., and AstraZeneca and has received grant support from the American Cancer Society related to nonsteroidal antiandrogens. Dr. Sartor has been a consultant to Schering-Plough, Inc.

Acknowledgments: The authors thank Chris Gonzalez, MD, and Nicholas Slimack, BA, for assistance with case reviews.

References

Infliximab-Induced Systemic Lupus Erythematosus

TO THE EDITOR: Infliximab is a chimeric mouse–human monoclonal antibody recently approved by the U.S. Food and Drug Administration for the treatment of both refractory Crohn disease and rheumatoid arthritis. By directly targeting tumor necrosis factor, this new agent has allowed reduction in steroid doses and has led to improvement in the clinical signs and symptoms of inflammation. We report the development of systemic lupus erythematosus after two infusions of infliximab in a patient with Crohn disease.

A 51-year-old woman with a 4-year history of Crohn colitis experienced a flare-up despite maintenance therapy with mesalamine and mercaptopurine. Mercaptopurine therapy was discontinued because of subtherapeutic levels. The patient began receiving infliximab, 5 mg/kg of body weight, and had an initial complete response. After a second infusion for a flare-up of symptoms, she developed diffuse inflammatory arthritis involving her hands, wrists, and shoulders. Serologic evaluation revealed leukopenia, antibodies to nuclear antigens (dilutions of 1:1280), antihistone protein, and elevated levels of double-stranded DNA antibodies by Farr assay. Drug-induced systemic lupus erythematosus was diagnosed. Further infusions of

Table. Patients with Prostate Cancer Who Developed Hypersensitivity Pneumonitis after Initiation of Nonsteroidal Antiandrogen Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bicalutamide</th>
<th>Flutamide</th>
<th>Nilutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>Median age (range), y</td>
<td>73.5 (59–91)</td>
<td>75.0 (65–84)</td>
<td>73.0 (45–89)</td>
</tr>
<tr>
<td>Median time receiving drug (range), wk</td>
<td>7.5 (1–312)</td>
<td>5 (1–156)</td>
<td>8 (1–182)</td>
</tr>
<tr>
<td>Patients whose reporting physician attributed pneumonitis to the nonsteroidal antiandrogen, n (%)</td>
<td>9 (75)</td>
<td>6 (38)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Patients receiving nonsteroidal antiandrogen monotherapy, n (%)</td>
<td>1 (8.3)</td>
<td>4 (25)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Patients who died of respiratory failure, n (%)</td>
<td>3 (25)</td>
<td>7 (44)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

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infliximab were discontinued, resulting in resolution of both leukopenia and arthritis.

Tumor necrosis factor seems to play a key role in host defense and immune surveillance (1). Although the development of antibodies to double-stranded DNA has been reported in up to 16% of patients treated with infliximab, clinically relevant systemic lupus erythematosus is extremely rare (2). In placebo-controlled trials of infliximab, 5 of 2292 patients receiving infliximab (2 with rheumatoid arthritis and 3 with Crohn disease; 0.22%) developed a lupus-like syndrome that resolved with discontinuation of therapy with the drug (3). Our patient had no previous joint symptoms. Her symptoms were temporally associated with intravenous infliximab therapy and resolved after therapy was discontinued. Although long-term data support the tolerability and efficacy of anti–tumor necrosis factor therapy, we believe systemic lupus erythematosus should be considered in patients who develop leukopenia or arthritis after receiving intravenous infusions of infliximab.

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References

GENERAL COMMENTARY

Bioterrorism and Physicians

TO THE EDITOR: During October and November 2001, the intentional transmission of anthrax to persons in the United States riveted public attention on the use of biological agents as weapons (1). To date, these incidents have been limited to a few geographic areas and have involved only anthrax (2). However, the threat persists of additional attacks on a larger scale and with different agents. Bioterrorism differs from other forms of terrorism in that casualties are geographically and temporally dispersed based on the clinical incubation ranges of the agents used. In addition, health care providers, not law enforcement, public safety, or emergency personnel, are the first responders. Therefore, physicians must acquire knowledge of specific biological threats that will enable them to effectively diagnose and manage patients in their care and control the spread of infection.

This is a complex undertaking. Many of these infections initially present with nonspecific illnesses, making early diagnosis difficult, and many physicians are unfamiliar with the clinical presentations. In addition, because these agents are manipulated in laboratories, their clinical presentation may not match that described in the extant literature.

People tend to view their personal physician as the most trusted source of information about bioterrorism (3). Physicians must therefore keep abreast of information in what continues to be an evolving situation. We must acknowledge our role as caretakers of the public health and must work in tandem with law enforcement and public health authorities to optimize public safety. Within our communities and hospitals, we should assume leadership roles to proactively develop and maintain contingency plans for managing the complex medical issues related to bioterrorism. We must remain vigilant for the possibility of additional attacks because these weapons are likely to pose persistent threats for the foreseeable future. Most important, we should live bravely and thus be leaders in these troubled times.

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References

CORRECTION

Correction: Articles on Diagnostic Tests

In a recent editorial introducing a new series on diagnostic tests (1), one of the authors’ affiliations was inadvertently omitted. Alan M. Garber, MD, PhD, is affiliated with the Veterans Affairs Palo Alto Health Care System, Palo Alto, California, as well as Stanford University.

Reference