Correspondence

Prophylactic Mastectomy in Carriers of *BRCA* Mutations

To the Editor: At first glance, the data of Meijers-Heijboer and colleagues (July 19 issue)[1] appear to support the position that prophylactic mastectomy reduces the risk of breast cancer in carriers of a *BRCA* mutation. On close reading of the article, however, I find that very little support for this position is presented. The authors report no new cases of breast cancer after a mean of 2.9 years in a cohort of 76 women who underwent mastectomy. This is to be expected, however; no breast cancers were detected on pathological review of the corresponding specimens, and it is exceedingly unlikely that a submicroscopic breast cancer will present as a chest-wall primary tumor or as metastatic disease within three years.

In a short-term follow-up study, it is perhaps possible to study whether or not preclinical breast cancers that are identified by pathological review are cured, but the investigators found no cancers. This is probably due to the small sample, the use of premastectomy screening examinations, and the high frequency of previous oophorectomy in the mastectomy group (58 percent). Oophorectomy prior to menopause reduces the incidence of breast cancer by 70 percent in carriers of a *BRCA1* mutation.[2]

My colleagues and I recently used magnetic resonance imaging (MRI) to perform screening examinations in 96 asymptomatic women with a *BRCA* mutation and detected five invasive breast cancers (prevalence, 5.2 percent) in this group.[3] To evaluate the ultimate effectiveness of MRI, it will be necessary to establish whether these women are eventually cured of their disease. If our figures are correct, then in the study by Meijers-Heijboer et al. there should have been four breast cancers among the women in the mastectomy group, and it is perhaps not surprising that none of these cancers were detected. But if the study was too small to allow detection of any breast cancers at the initial pathological review, then it was too small to evaluate the effectiveness of mastectomy as a prophylactic measure over the short term. At the Centre for Research in Women's Health at the University of Toronto, I have prospectively studied a cohort of 61 carriers of a *BRCA* mutation after prophylactic mastectomy for a mean follow-up period of three years and have collected data on new cancers in this cohort. I intend to submit the data for publication when the results are interpretable.

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1. Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in women with a *BRCA1* or *BRCA2* mutation. N Engl J Med 2001;345:159-64.
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To the Editor: In the article by Meijers-Heijboer et al., a 10-to-15-year mortality rate of 35 to 50 percent is projected for those whose hereditary breast cancers are diagnosed by surveillance. Since the authors state that the prognosis of *BRCA*-associated tumors is no different than that of non–*BRCA*-associated tumors, the poor outcome they project for women who choose surveillance must be due to the stage of the cancers in carriers of a *BRCA* mutation. However, in contrast to the 50 percent rate of lymph-node metastasis in this study, other studies have reported a 21 percent rate: in two separate MRI series involving a combined total of 375 women at hereditary risk for breast cancer, only 4 of 19 detected breast tumors were lymph-node positive.[1,2] The 25 percent 10-year risk of breast cancer assumed in the current, clinic-based series is also higher than the rate we and others have derived from ascertainments not biased by family history.[3]

Varying these two assumptions would result in a substantially lower projected mortality in women undergoing

risk-reducing mastectomy as compared with surveillance. Even assuming a 10-year incidence of breast cancer of 25 percent, 75 percent of the women who opt for preventive surgery would not have breast cancer during this period.

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1. Stoutjesdijk MJ, Boetes C, Jager GJ, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001;93:1095-102.
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To the Editor: Meijers-Heijboer et al. found no instance of breast cancer after prophylactic bilateral mastectomy among 76 women followed for 219 women-years at risk. An exponential model was used to estimate the annual risk among 63 other women, who chose to remain under surveillance and were followed for 190 women-years; in this group, eight cases of breast cancer developed, and the annual rate of breast cancer was estimated at 2.5 percent. No estimate was given for the prophylactic-mastectomy group.

Unfortunately, the finding of zero cases does not imply that the risk is zero.[1] The data are compatible with a very small annual risk not detectable during 219 women-years of follow-up. An estimate of the upper limit of the annual risk can be made by using an exponential model (with a constant hazard rate), assuming independence of the events, and specifying the desired power. At a power of 0.80, 0.90, or 0.95, the respective upper limits are 0.73 percent, 1.05 percent, and 1.36 percent per year. To compare these estimates with that in the surveillance group, we also must assume that our ability to detect breast cancer (i.e., the sensitivity of our methods of detection) is the same for both groups.

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1. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249:1743-5.

To the Editor: In their article on prophylactic mastectomy in women with a *BRCA1* or *BRCA2* mutation, Meijers-Heijboer and colleagues "estimate that 10 to 20 percent of women who choose surveillance will die of breast cancer within 20 years." Our own recent findings[1] and those of others[2,3] suggest that the inclusion of MRI in surveillance programs will allow earlier detection of breast cancer in such women. This approach will most likely result in a lower mortality than the estimate that Meijers-Heijboer and colleagues make. In studies that compare the efficacy of options open to women with a hereditary risk of breast cancer, the addition of MRI to the surveillance program of each woman is therefore essential.

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The authors reply:

To the Editor: The aim of our study was not to investigate the process of tumor progression, as suggested by Narod, but to estimate the reduction of risk by prophylactic mastectomy in healthy women with a *BRCA1* or *BRCA2* mutation as compared with that in similar women who opted for surveillance after the possibility of an existing tumor was ruled out (one woman was found to have breast cancer at the first screening and was excluded from the study). This risk reduction appeared to be significant, even after adjustment for past oophorectomy. Because all the women underwent premastectomy screening examinations to rule out breast cancer, it was not surprising that only one carcinoma in situ was found in the specimens obtained at the time of mastectomy. The series of women with a *BRCA1* or *BRCA2* mutation in the MRI study conducted by Narod's group[1] cannot be compared with our series. The women in their series were older and had a different spectrum of *BRCA1* and *BRCA2* mutations; 34 (35 percent) had a history of breast cancer (four of the seven cancers detected were found in the contralateral breast of affected women); 29 percent had not undergone screening mammography within the previous 15 months; the number of new cancers was unclear; and the median follow-up was very short (1½ years or less).

As suggested by Offit et al., the risk in women in population studies might differ from that in women with a family history. However, because in our family cancer clinic we see mainly women who are worried by their family history, we decided not to enter into a discussion of data from population studies.

The clinical outcome we projected for the women who chose surveillance was based not only on stage but also on their young age and on the unfavorable pathological characteristics of *BRCA1*-associated breast cancers. Previously we reported a 50 percent death rate after 10 years in women with primary breast cancer who had either a *BRCA1* mutation[2] or a *BRCA2* mutation.[3] In addition, in a series of 1198 women at high risk, we found that the screening results were worse in women in the youngest age category and in those with a *BRCA1* or *BRCA2* mutation than in women in other subgroups.[4]

We agree with Offit et al. and Stoutjesdijk and Barentsz that the application of sensitive MRI methods in a standard surveillance program might improve survival, but hard

data are lacking. Finally, we thank Riggs for his interesting calculations and agree that encountering zero cases does not imply that the risk is zero, as indicated by the 95 percent confidence interval of 0 to 0.36 in our report.

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1. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol 2001;19:3524-31.
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Treatment of Hairy-Cell Leukemia

To the Editor: Kreitman et al. (July 26 issue)[1] report that an anti-CD22 recombinant immunotoxin (BL22) induced complete remissions in 11 of 16 patients with hairy-cell leukemia that was resistant to cladribine. Although BL22 represents an exciting new approach to the treatment of this disease, the results need to be interpreted cautiously, given the potential life-threatening toxicity of this agent (the hemolytic–uremic syndrome developed in two patients).

When a single course of cladribine was administered by continuous intravenous infusion for seven days to 349 patients with hairy-cell leukemia at Scripps Clinic, 319 patients (91 percent) had an initial complete response, and 22 (6 percent) had a partial response.[2] Ninety patients (26 percent) relapsed after a median of 29 months. Of 53 patients treated with second courses of cladribine at the time of the first relapse, 33 (62 percent) had complete responses, and 14 (26 percent) had partial responses. Thus, cladribine resistance in patients with hairy-cell leukemia is indeed a rare occurrence. Kreitman et al. should therefore clarify their definition of cladribine resistance as "an inadequate response." Also, despite the structural and mechanistic homology between cladribine and pentostatin (2′-deoxycoformycin), cladribine induced durable complete responses in patients with hairy-cell leukemia that was truly resistant to pentostatin, suggesting the absence of cross-resistance between these two agents.[3]

The 16 patients of Kreitman et al. had hairy-cell leukemia with an unusual resistance to systemic chemotherapy. The features predicting this resistance were the marked lymphocytosis in five patients, the abdominal masses in two patients, and the aberrant display of CD antigens in three patients.[4]

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Editor's note: Dr. Saven is a consultant to SnowBrand Pharmaceuticals, focusing on the clinical development of BL22, and has received grant support from Ortho Biotech.

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4. Tetreault SA, Robbins BA, Saven A. Treatment of hairy cell leukemia-variant with cladribine. Leuk Lymphoma 1999;35:347-54.

The authors reply:

To the Editor: All 16 patients with hairy-cell leukemia in our study had an inadequate response to their last treatment with cladribine. Two had brief complete remissions that lasted 4 and 15 months. The other 14 patients had a partial response or no response to the last course of cladribine, and in only 1 of them was the cytopenia corrected. Five patients had no response to the first course of cladribine, an unusual finding in patients with hairy-cell leukemia, whereas 11 patients had resistance to cladribine after one to five relapses, a more typical finding. We agree with Saven that cladribine is associated with a high rate of complete remission in patients who have not previously been treated and in those with a first relapse, but almost 5 percent of patients have no response or have persistent cytopenia after their first course of cladribine.[1] Furthermore, the rate of complete remission and the time to treatment failure decrease with subsequent courses of the drug, and there is no plateau in disease-free or overall survival.[2-4]

Long-term follow-up data after three or more courses of cladribine have not been published. The median follow-up in the study cited by Saven was 58 months, and the study ended in mid-1987.[1] No other trial has reported longer follow-up data. In contrast, our patients were enrolled a median of eight years after diagnosis, and most had received other treatments in addition to cladribine. The 11 patients in our study who had received more than one course of cladribine began BL22 treatment 2 to 10 years (median, 7) after the first course of cladribine.

We believe that BL22 is a potentially important investigational therapy for cladribine-resistant hairy-cell leukemia, since it produces complete remission without irreversible toxicity.

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Management of Tuberculosis

To the Editor: When discussing indications for the treatment of latent tuberculosis infection, Small and Fujiwara (July 19 issue)[1] follow the joint statement of the American Thoracic Society and the Centers for Disease Control and Prevention (CDC)[2] in considering patients regardless of age. Prior guidelines did not recommend routine treatment for those older than 35 years, the point at which isoniazid hepatotoxicity was thought to be more likely to occur than disease reactivation.[3] Is age no longer a concern? For example, since treatment is now recommended for all tuberculin-positive persons who have emigrated from high-prevalence areas to the United States within the preceding five years, should we prescribe isoniazid to a recently arrived 75-year-old person? Should we withhold therapy from a 26-year-old who came to the United States at the age of 19?

Small and Fujiwara also recommend initial two-step testing for persons who are likely to have serial tuberculin tests, to avoid confusion from future false positive "conversions" caused by the booster phenomenon. As they note, such results imply waning immunity from infections acquired in the distant past. Yet the CDC recommends that all newly employed health care workers receive two-step testing if they lack proof that they have had a negative skin test within the preceding 12 months,[4] despite the added expense and inconvenience. Is this step required for low-risk employees? What if one had a negative skin test two or three years previously? Would a 25-year-old employee who had been born in a high-prevalence area even require two-step testing, since the booster phenomenon is rare at this age?

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To the Editor: Small and Fujiwara mention the possibility of eliminating tuberculosis in the United States. For this to become a reality, however, "hot spots" of tuberculosis, especially in the South and in urban areas, will need to be addressed by public health officials. Nearly all southeastern states continue to have rates of tuberculosis that are higher than the national average, with most cases occurring among U.S.-born persons, most frequently blacks.[1,2] In Georgia, the number of cases of tuberculosis has increased in the past two years.[1] The rates of disease in some areas of Atlanta exceed 100 cases per 100,000 persons per year,[3] similar to the rates in developing countries.

TABLE 1. CASES OF TUBERCULOSIS REPORTED IN THE UNITED STATES, GEORGIA, AND GRADY MEMORIAL HOSPITAL IN ATLANTA.

YEAR	UNITED STATES*	GEORGIA*	GRADY MEMORIAL HOSPITAL
	number of cases		
1996	21,337	791	175
1997	19,851	691	175
1998	18,361	636	142
1999	17,531	665	148
2000	16,377	703	139

*Data are from the Centers for Disease Control and Prevention.[1]

The racial disparity is also striking, with rates that are 12 times as high among blacks as among whites. This high burden of disease greatly affects Grady Memorial Hospital, where active tuberculosis was diagnosed in 139 patients (a third of whom were coinfected with the human immunodeficiency virus) in 2000, for a rate of 496 cases per 100,000 admissions (Table 1). During the past decade, if Grady Memorial Hospital had been a state, it would have ranked 28th in the country in terms of the number of cases reported.[3] Tuberculosis is not a Medicaid-eligible disease in Georgia (as it is in all of the other high-incidence states); thus, the hospital has annually provided more than $1.5 million of uncompensated care to patients with tuberculosis.

Adequate resources for care, public health control, and research on interventions to interrupt the transmission of *Mycobacterium tuberculosis* in hot spots are much needed and will be required if we are serious about eliminating tuberculosis in the United States.

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To the Editor: In their otherwise excellent review of tuberculosis, Small and Fujiwara did not adequately address the difficult subject of the use of rifampin with nonnucleoside reverse-transcriptase inhibitors. There is no change in rifampin levels when it is given with either of the two most commonly prescribed nonnucleoside reverse-transcriptase inhibitors, nevirapine and efavirenz.[1,2] Small and Fujiwara appropriately note that delavirdine and nevirapine, the first two of these agents to be approved by the Food and Drug

Administration, are not recommended for use with rifampin because rifampin can significantly lower serum levels of these antiretroviral agents. However, rifampin reduces the area under the curve, minimal concentration, and maximal concentration of efavirenz, the most recently approved nonnucleoside reverse-transcriptase inhibitor, by less than 30 percent in all studies published to date.[2,3] Hence, many experts recommend the combination of rifampin and efavirenz, with an increase in the dose of efavirenz to 800 mg per day, for the treatment of patients with tuberculosis who require antiretroviral therapy.[2,3] One small study even compared a regimen of efavirenz and rifampin with a regimen of rifampin alone and found that both regimens were highly efficacious.[4]

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To the Editor: Small and Fujiwara state that evaluation of urine for discoloration can be used to assess compliance in patients who are taking rifampin for tuberculosis. Because of its pharmacokinetics, isoniazid is also suitable for use in an assessment of compliance. The "Arkansas method" for the detection of isoniazid allows compliance to be assessed even if patients took the drug up to 24 hours before their arrival at the clinic.[1,2] The peak of the rifampin-induced orange coloration of the urine occurs six hours after the ingestion of the drug. This test lacks specificity and sensitivity if it is performed more than 12 hours after the ingestion of rifampin.[3] The Arkansas method has equally good results with the use of commercially available paper strips (Taxo INH test strips, Becton Dickinson, Cowley, United Kingdom) or dipsticks made in any laboratory.[4]

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Dr. Small replies:

To the Editor: I appreciate the valid comments made by each of the correspondents, the spectrum of which emphasizes the complexities of managing tuberculosis in the current era. Some of this complexity arises from the intrinsic challenges of translating treatment guidelines into clinical practice. For example, Mr. Leiner asks whether, given the de-emphasis of age as a criterion for treating latent tuberculosis infection, I would "prescribe isoniazid to a recently arrived 75-year-old" immigrant. Perhaps, depending on the details. In general, I might not, but I certainly would if the person were at high risk for progression to active disease (such persons are a group for which there has never been an age cutoff).

An important resource for assistance in working through the details of specific situations is the "tuberculosis warmlines" funded in part by the CDC (415-502-4700 or 800-4TB-DOCS). Health care providers who dial these numbers will be connected within 24 hours to a tuberculosis expert with whom they may discuss individual situations.

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More on Pamidronate in Langerhans'-Cell Histiocytosis

To the Editor: Arzoo et al. (July 19 issue)[1] report on a 23-year-old woman with Langerhans'-cell histiocytosis and severe pain due to osteolytic lesions, who had a good response to a 90-mg infusion of pamidronate. Although the literature on the use of pamidronate in patients with Langerhans'-cell histiocytosis is scarce, there have been previous observations.[2-4]

Elomaa and coworkers reported that the use of pamidronate (1.6 g per day orally for six months) in two adults with multifocal eosinophilic granuloma resulted in pain relief, regression of lesions, and biochemical evidence of decreased bone resorption.[2] Recently, my colleagues and I reported our experience in treating a 14-year-old boy who had long-standing multisystem Langerhans'-cell histiocytosis with multifocal bone pain, which was unresponsive to chemotherapy, corticosteroids, antiinflammatory agents, and narcotic analgesics.[3] He had a response to two cycles of intravenous pamidronate, each of which consisted of 90 mg per day given on three consecutive days. Two subsequent episodes of deterioration responded to the same treatment. The use of bisphosphonates in the treatment of pulmonary Langerhans'-cell histiocytosis was also recently suggested, on the basis of their relative safety and their documented antimacrophage activity.[4]

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To the Editor: The observation by Arzoo et al. that pamidronate therapy was effective in relieving bone pain in their patient with osteolytic Langerhans'-cell histiocytosis is consistent with both the pharmacologic action of aminobisphosphonates in this context and the biochemistry of Langerhans'-cell histiocytosis. Nitrogen-containing bisphosphonates inhibit the mevalonate pathway, leading to the reduced formation and function of osteoclasts and to their apoptosis.[1,2] Thus, one would expect pamidronate to be effective in relieving bone pain in patients with osteolytic Langerhans'-cell histiocytosis, given the identification of components of the mevalonate pathway in this disease. Specifically, the earlier report of a preponderance of cholesterol esters in histiocytosis X cells[3] and my recent detection of the α subunit of both farnesyltransferase and geranylgeranyltransferase in osteolytic lesions from patients with Langerhans'-cell histiocytosis (Fig. 1) provide evidence of the mevalonate pathway in osteolytic Langerhans'-cell histiocytosis and support the reported observation by Arzoo et al.

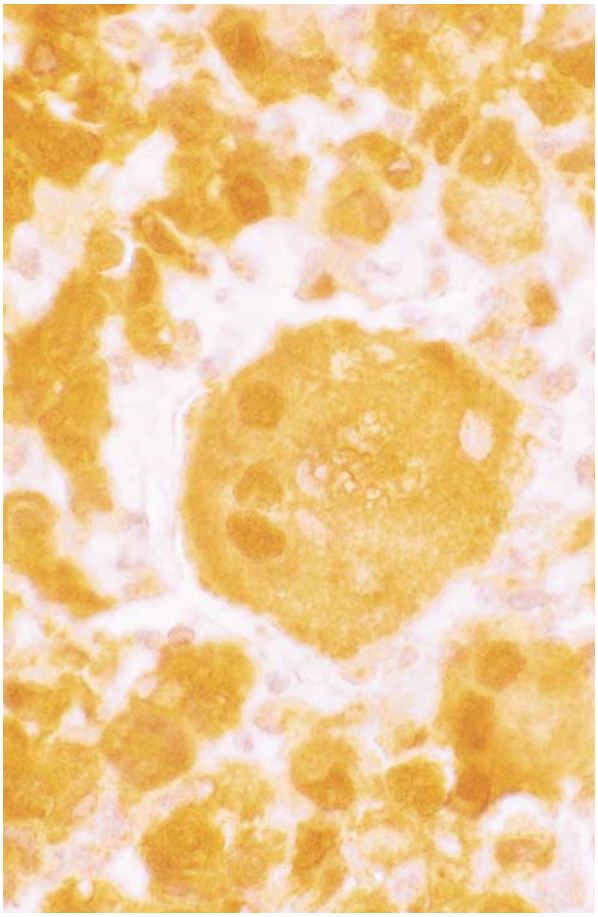

Figure 1. Immunohistochemical Detection of the α Subunit Common to Farnesyltransferase and Geranylgeranyltransferase of Human Origin in an Osteolytic Lesion from a Patient with Langerhans'-Cell Histiocytosis (3-3′Diaminobenzidine Tetrahydrochloride Chromogen, ×788).

The strong staining (brown chromogen) in both the multinucleated, osteoclast-like giant cells and the lesional histiocytes is indicative of the presence of this antigen in Langerhans'-cell histiocytosis and, therefore, of the branching point of the mevalonate pathway,[4] which leads to both prenylation of proteins and cholesterol synthesis.

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Vesical Varices in a Patient with Portal Hypertension

To the Editor: Portal hypertension is a frequent consequence of cirrhosis and may lead to dilated venous collaterals. Usually, varices due to portal hypertension develop in the lower esophagus, stomach, or rectum and rarely in other parts of the digestive tract.[1] Extraintestinal ectopic varices are very rare. We recently treated a patient with cirrhosis who had gross hematuria from vesical varices.

A 54-year-old woman with ongoing alcohol abuse had a sudden onset of profuse gross hematuria. She had a history of alcoholic liver cirrhosis, complicated by decompensated ascites and ruptures of esophageal varices, and chronic pancreatitis. She had undergone sclerotherapy and band ligation for the management of varices. Her history was also notable for cholecystectomy, radical left nephrectomy for renal-cell carcinoma, and hysterectomy. Her hematuria had stopped by the time she was admitted.

Abdominal ultrasonography showed multiple nonechogenic nodes in the superior and posterior wall of the bladder. Cystoscopy demonstrated large vesical varices (Fig. 1). Selective angiography of the superior mesenteric artery revealed venous dilatations at the root of the mesentery, in the ileal and colonic region, which drained to large vesical varices and then to the right internal and external iliac veins. The patient was treated with propranolol, which is used to treat patients with cirrhosis and variceal hemorrhage. There was no recurrence of hematuria during one year of follow-up.

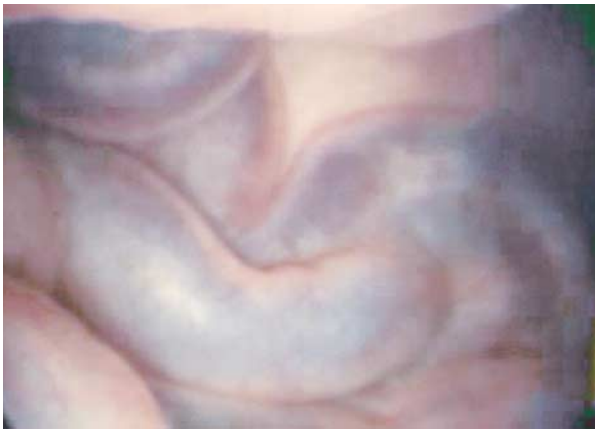

Figure 1. Cystoscopic Findings Demonstrating Varices on the Posterior Wall of the Bladder.

Vesical varices secondary to portal hypertension are rare, since the bladder wall is an unusual collateral route for the venous splanchnic blood. Vesical varices may appear when the usual splanchnic-bed collaterals cannot develop,[2] thus allowing venous blood to flow through the venous system of the bladder. Since our patient had a history of sclerotherapy, band ligation, and abdominal surgery, her usual venous collaterals may have been interrupted.

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From a Physician in Lower Manhattan

To the Editor: I have a private practice, with two other family physicians, in an office in the financial district of lower Manhattan, five blocks (300 m) from the site of the World Trade Center. Most of our patients work or live in lower Manhattan, including many who worked in the World Trade Center or its vicinity. We have learned of the deaths of at least four of our patients who were trapped in the collapse of the World Trade Center towers on September 11.

At the time of the attacks, our office had just opened for the day. (I was on the New York City subway, which had been stopped shortly after the crash of the first airplane.) Within minutes after the crash of the second airplane, when the nature of the attacks became clear, much of lower Manhattan, including our office, was evacuated. There was considerable fear and anxiety, particularly about the prospect of further attacks, but everyone was evacuated safely.

Federal and city authorities kept lower Manhattan evacuated, except for emergency personnel, for six days after the attacks. Electricity and telephone service remained disrupted, and sanitation crews cleaned tons of debris and thick dust from the streets and building facades. We kept in touch with many of our patients by means of an e-mail list we maintain. Patients contacted me by e-mail, as well as by telephone, at our satellite office in midtown Manhattan. A state of shock and grief pervaded New York in the first weeks after the tragedy. The most common requests from patients were for refills of existing prescriptions. Many patients had been evacuated from their homes and had left their medications behind. Others depended on pharmacies that were closed. One popular pharmacy was destroyed in the collapse of the buildings.

During the second week after we had reopened our office, the psychic consequences of the tragedy became clear in the problems our patients reported. Many reported insomnia, difficulty concentrating, nightmares, fear of reentering the vicinity of the attacks, and tearfulness. Most accepted prescriptions for antidepressants, anxiolytic agents, and hypnotic agents. Many accepted referrals to mental health professionals, who were overwhelmed with calls but remained available during the crisis. Somatic manifestations of posttraumatic stress were common.

Patients told of narrow escapes from the buildings, attempts to outrun the thick plume of debris that rapidly filled the canyon-like streets of New York. They told of witnessing people jump from the tops of the towers, and they told of seeing bodies and body parts. Others told of the loss of friends and family members who had worked in the World Trade Center. One patient lost seven coworkers. Another counted among the dead 17 colleagues at the Fuji Bank in the World Trade Center.

Over a month after the tragedy, New Yorkers are still preoccupied with thoughts of the disaster, despite pleas by the mayor for a return to normalcy. Most of our patients continue to express their fears, and many continue to experience depression and anxiety.

The attacks of September 11 were unprecedented. Unfortunately, there is now a lot to learn in lower Manhattan about the medical and psychiatric consequences of terrorism.

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