Letters

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Transmission of Hepatitis C Virus to Spouses

To the Editor: Akahane and colleagues (1) reported that 27% of spouses of patients with hepatitis C virus (HCV) infection had antibodies against HCV and that 18% of the spouses were positive for HCV RNA. Bresters and colleagues (2) observed no sexual transmission in 50 heterosexual partners of index patients positive for HCV RNA who had had unprotected sexual intercourse for a total of 713 person-years (mean duration per couple, 13 years). In this study (2), branched-chain DNA assay showed that index patients had an HCV RNA titer ranging from below the cutoff to 626×10^5 eq/mL, which is similar to titers found in Asia (3). Unfortunately, no HCV RNA titers were determined in Akahane and colleagues' study and, therefore, no conclusions can be made about the importance of viral load in relation to sexual transmission.

Persons with HCV subtype II (1b) are more common in Asia than in Europe and the United States. Bresters and colleagues, however, found HCV type II in 59% of persons with hemophilia (n = 39) compared with 20% of those without hemophilia (Cuypers HT. Personal communication). Therefore, as indicated by Akahane and colleagues, subtype II may not be a substantial risk factor for HCV transmission. The possible cause of HCV infection in index patients was not stated in the report by Akahane and coworkers. In most index patients, if no source of infection is found, this result may suggest that the source of infection is the same for the spouse, which also explains the concordance of HCV subtypes in couples.

Polymerase chain reaction (PCR) assays at present have a low specificity (4). It is remarkable that 2 of 27 (7.4%) spouses were positive for HCV RNA in the absence of HCV antibodies. This is an extremely rare finding and, so far, has only been observed in patients with acute HCV infection and in immunosuppressed patients. Therefore, one may question whether Akahane and coworkers' data are influenced by the specificity of their PCR assay. Future studies on sexual transmission of HCV should be done in low-endemic areas and should include well-characterized HCV-infected persons with a relatively short (<10 years) duration of sexual relationship.

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3. **Hsu HH, Wright TL, Luba D, Martin M, Feinstone SM, Garcia G, et al.** Failure to detect hepatitis C virus genome in human secretions with the polymerase chain reaction. Hepatology. 1991;14:763-7.
4. **Zaayer HL, Cuypers HT, Reesink HW, Winkel IN, Gerken G, Lelie PN.** Reliability of polymerase chain reaction for detection of hepatitis C virus. Lancet. 1992;341:722-4.

In response: No HCV infection developed in any of seven spouses of patients with chronic hepatitis C during the first 10 years after marriage in our study. This finding is in agreement with the observation of Mauser-Bunschoten and colleagues that persons with hemophilia who were positive for HCV RNA did not transmit HCV to their 50 heterosexual partners within a mean duration of 13 years. The absence of transmission within the first decade of a heterosexual relationship, however, does not guarantee that transmission will not occur in the future. Our principal message is that spouses of patients with chronic hepatitis C are at high risk for HCV infection and that this risk increases with the duration of marriage (calibrated in decades).

Among family members of patients with chronic hepatitis C, spouses are at the highest risk for infection (1). Because marriage involves various close body contacts other than the sexual relationship, it is possible that sexual relations may not be exclusively implicated in the observed high prevalence of HCV infection in spouses of patients. Nonetheless, sexual contact distinguishes spouses from the other members of the family, and spouses stay together much longer than do any of the other members. As mentioned in our report, no common source infection was identifiable in the patient–spouse pairs we studied. Intravenous drug use is rare in Japan, as is folk medicine involving skin puncture with shared instruments.

We disagree with the statement of Mauser-Bunschoten and colleagues that genotype II (1b) may not be a substantial risk factor for HCV infection. Our experience, and that of others (2, 3), is that HCV genotype II (1b) causes higher HCV RNA levels than do the other HCV genotypes. The detection of HCV RNA in the absence of HCV antibodies is not an extremely rare finding as proposed by Mauser-Buschoten and colleagues. Of 59 patients with post-transfusion hepatitis C, 4 (6.7%) received blood units that tested negative for HCV when the second-generation enzyme immunoassay was used (4), thereby indicating that seronegative HCV viremia is not extremely rare, even among the general population. Thus, it may not be so remarkable that 2 of 27 (7.4%) spouses in our study were positive for HCV RNA in the absence of antibodies to HCV, and this result does not arouse concern about the specificity of our PCR assay.

Once again, we recommend that spouses of patients with hepatitis C be followed for markers of HCV infection, so that efficient therapeutic intervention can be provided when necessary.

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Screening for Ovarian Cancer

To the Editor: The clinical guideline and review article on screening for ovarian cancer are concise, clear statements about this particular issue (1, 2). As a practicing clinician, I appreciate the effort to provide guidance for a rational clinical approach to screening testing.

One gray area related to this problem is the need for pelvic examinations in healthy, asymptomatic, previously screened (for cervical cancer) women between Papanicolaou tests. I generally do Papanicolaou tests every 3 years in my patients after establishing two or three normal test results within a year. How often pelvic examinations need to be done exemplifies the problem of "complete physical examinations versus screening examinations." The practical significance of this question is the amount of time that must be allotted for doing screening maneuvers and the ability to integrate this screening into routine office visits.

I have two questions for the authors. First, is there a justification or rationale for doing pelvic examinations in healthy, asymptomatic, previously screened women? Second, as a practical matter, do the authors do pelvic examinations on a more frequent basis than is required for Papanicolaou testing in healthy, asymptomatic, previously screened women?

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In response: One reason for doing a bimanual pelvic examination to screen for ovarian cancer in asymptomatic women is the possibility that a highly skilled examiner may detect early-stage ovarian cancer, although only limited scientific evidence suggests that even highly skilled examiners can detect this cancer. Lacking better data, our clinical practice is to make an individualized decision about how frequently to do a screening bimanual pelvic examination for each woman. This decision considers the patient's risk factors for ovarian cancer, preferences, factors affecting the accuracy of the examination (such as obesity), and comorbid illnesses and their complexity. In practice, the need to do a pelvic examination for other clinical reasons frequently provides an opportunity to examine the ovaries periodically.

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Prinzmetal Angina and Cyproheptadine

To the Editor: Schecter and colleagues (1) reported that a subset of patients with Prinzmetal angina who were refractory to nitrites and calcium channel blockers responded to the antiserotonergic agent cyproheptadine. Little information is available on the mechanisms of action involved or on why some other antiserotonergic agents were inactive in this disorder.

In an earlier study (2), we found that cyproheptadine substantially inhibited platelet aggregation in vivo, ex vivo, and in vitro. It inhibited both serotonin and adenosine diphosphate–induced aggregation. The agent also has antihistamine activity. Inhibition of platelet aggregation may break the vicious cycle in which serotonin is released from aggregating platelets on arteriosclerotic plaques causing more platelet aggregation and more serotonin release. These relatively high concentrations of serotonin then interact with arteriosclerosis-altered vascular walls, thus causing vasospasm.

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2. **Ambrus JL, Ambrus CM, Thurber LE.** Study of platelet aggregation in vivo. V. Effect of the antiserotonin agent cyproheptadine. J Med. 1977;8:287-94.

In response: Dr. Ambrus emphasizes that inhibition of platelet aggregation is a potential important pathophysiologic mechanism for serotonergic-receptor blockade in vasospasm. Serotonin is initially released when platelets aggregate and initiate a positive feedback loop by releasing adenosine diphosphate, thromboxane A_2, and more serotonin.

An early study (1) failed to show a decrease in the number of ischemic episodes in patients with vasospastic angina who were treated with ketanserin, a selective serotonin-receptor (S_2) antagonist. Ketanserin was given at concentrations that inhibited in vitro platelet aggregation. The presence of serotonin-receptor families, individual patient characteristics for platelet aggregation, and differing in vivo responses may make the use of other serotonin-receptor antagonists, such as cyproheptadine, clinically efficacious in selected patients.

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Reference

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Fasciitis and Fasciitis–Panniculitis in Chronic Graft-versus-Host Disease

To the Editor: Janin and colleagues (1) described 14 patients with fasciitis who had chronic graft-versus-host disease. Their patients had a disease that resembled eosinophilic fasciitis. Biopsy specimens showed that the earliest histologic changes were edema and fibrosis in the intermediate septa separating the fat lobules and in the muscular fascia beneath the fat lobules.

After the characteristics of eosinophilic fasciitis (a disorder of unknown cause) were described, similar clinical and histologic features were noted to occur in patients with various diseases, such as morphea profunda, lupus erythematosus panniculitis, the toxic oil syndrome, the eosinophilia-myalgia syndrome, postirradiation injury, infections, cancer, venous or lymphatic diseases, and graft-versus-host disease (2–4). When any of these disorders are referred to, the term "fasciitis" has been used based on the assumption that the inflammatory reaction arises in the fascia, spreading to the septa of the subcutaneous fat tissue.

In a series of 32 patients (3), the histologic features of eosinophilic fasciitis were compared with those features of extensive subcutaneous induration as a manifestation of other diseases (infectious, paraneoplastic, post-traumatic, and circulatory disorders). Evidence from this investigation (3) challenges the notion that the first histologic alteration takes place in the fascia. Indeed, all biopsy specimens showing features of fasciitis also showed evidence of septal panniculitis. However, cutaneomuscular biopsy specimens obtained from the periphery of a lesion often showed septal panniculitis but a normal fascia (3). When multiple indurative lesions coexisted, cutaneomuscular biopsy specimens taken from small lesions indicated either septal panniculitis or panniculitis and fasciitis. Samples from larger lesions always showed panniculitis and fasciitis. These data (3) suggest that the intermediate septa are the first to be affected by the inflammatory sclerosing process, whereas the fasciitis is secondary to the spread of inflammation to the fascia. Other authors (5) believe that simultaneous involvement of the fascia and the subcutaneous septa occurs from the onset. If this hypothesis is correct, then, in view of our findings, the fasciitis has a segmental distribution, "skip lesions" alternating with segments of normal fascia.

Many noxious agents may induce panniculitis associated with fasciitis. Hence, the term "fasciitis–panniculitis syndrome" has been proposed (3) when referring to the clinical manifestations and histologic alterations in the subcutaneous fascial layers shared by eosinophilic fasciitis and various other disorders. Fasciitis–panniculitis in graft-versus-host disease (Figure 1 in reference 1) rather than fasciitis in graft-versus-host disease is one of those disorders.

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In response: Naschitz and colleagues suggest that fasciitis–panniculitis would be a more appropriate term than fasciitis to qualify the lesions we described recently in graft-versus-host disease. Both terms refer to pathologic entities. As a pathologist, I insist that panniculitis, in the strict sense, applies to inflammation of fat lobes rather than to inflammation of interlobular septa or of large cutaneous vessels. The fetal development makes each fat lobe a separate organ with a nourishing artery and two draining veins, and this separation explains the sharp limitation of panicular inflammation (1). We did not find fat cell necrosis in any of our patients' biopsy specimens. The earliest histologic changes in our patients were indeed localized in the muscular fascia and the intermediate septa separating the fat lobules, but the changes did not involve fat cells. The initial change is not, therefore, a panniculitis.

Because one of the biopsy specimens was obtained only 17 days after the onset of the symptoms, the fascia was involved very early. Moreover, the different biopsy specimens, obtained 17 to 1015 days after the onset of the symptoms, showed that the fascia was constantly involved and that inflammation and fibrosis predominated within the fascia. Finally, although we agree that simultaneous involvement of the fascia and the subcutaneous septa can occur from the onset in fasciitis in patients with graft-versus-host disease, as in patients with eosinophilic fasciitis (2), we do not believe that "panniculitis" is the proper term for the associated inflammation and fibrosis limited to the subcutaneous septa.

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Chronic Severe Hemolytic Anemia from Phenazopyridine

To the Editor: The case report by Thomas and colleagues (1) is interesting. Phenazopyridine (Sedural or Pyridium), an azo dye, is not an over-the-counter drug. The other common medications having phenazopyridine in combination with sulfamethoxazole and sulfisoxazole are Azo Gantanol and Azo Gantrisin, respectively (2). None of the preparations of phenazopyridine is available over the counter. I wonder whether the patient or her husband was, in fact, getting the drug by "inadvertent" prescription.

Further, oxidative Heinz-body hemolytic anemia with "bite cells" (degmacytes) is well documented as occurring after chronic overdosing with phenazopyridine (2, 3). Glucose-6-phosphate dehydrogenase deficiency in erythrocytes may predispose patients to hemolysis. Acute hemolytic anemia after a single 1-g dose of phenazopyridine has also been described (4).

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1. **Thomas RJ, Doddabele S, Karnad AB.** Chronic severe hemolytic anemia related to surreptitious phenazopyridine abuse. Ann Intern Med. 1994;121:308.
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3. Drug: Facts and Comparisons. 48th ed. St. Louis: Wolter Kluwer; 1994:2881-2.
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To the Editor: Thomas and colleagues (1) recently described chronic severe hemolytic anemia related to phenazopyridine. We also previously reported (2) the potent oxidative hemolytic effect of phenazopyridine (Pyridium).

Our patient with a normal glucose-6-phosphate dehydrogenase level developed severe Heinz-body hemolytic anemia and developed sulfhemoglobinemia after prolonged treatment with phenazopyridine. The patient had a nadir hemoglobin level of 7.3 g/dL a reticulocyte count of 13%, and Heinz bodies in 20% of her erythrocytes.

In vitro studies with erythrocytes deficient in glucose-6-phosphate dehydrogenase showed that phenazopyridine has 50% of the oxidant capacity of the benchmark (standard) compound acetylphenyl hydrazine (2). It is useful to be aware of this adverse effect because phenazopyridine is frequently prescribed for various nonspecific urinary symptoms.

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In response: We stand corrected. Pyridium itself is not available over the counter. However, the pharmacist who notified us of our patient's drug habit confirmed that our patient did purchase more than 12 boxes per week of one of several preparations available over the counter (Azostandard, Polymedica Pharmaceutical Inc., Woburn, Massachusetts; Reazo, Reese Chemical, Cleveland, Ohio; and Baridium, Pfeiffer Co., Wilkes-Barre, Pennsylvania) that contain 95 to 100 mg of phenazopyridine hydrochloride per tablet (1, 2).

We had overlooked the classic paper by Gabor and colleagues (3) that was perhaps the first to thoroughly document hemolysis caused by phenazopyridine. Other reports (4) also describe Heinz-body hemolytic anemia as an acute or subacute phenomenon in the setting of renal failure. We believe that our patient, who had normal renal function, represents the first clearly documented case of severe chronic hemolytic anemia caused by the abuse of phenazopyridine in over-the-counter preparations. Finally, we agree with Dr. Gabor that it is important to highlight this unique toxic reaction of phenazopyridine because it is a commonly prescribed drug (Pyridium) in patients with various urinary tract symptoms. Its availability in over-the-counter preparations underscores the importance of recognizing signs of phenazopyridine toxicity—the syndrome of lemon-yellow skin color in the absence of jaundice, of hemolysis, and of bite cells on the blood smear. We salute the astute pharmacist who brought this to our attention.

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Joseph Goldberger: Unsung Hero

To the Editor: For his pellagra studies in the first quarter of this century, Joseph Goldberger is considered a hero (1). However, Goldberger deliberately induced pellagra in prisoners, and, in an attempt to show that pellagra was not infectious, he injected blood from patients with pellagra into volunteers and had them ingest feces from patients with pellagra. Elmore and Feinstein's opinion (1) is that the first study in prisoners, at least, is questionable: "This study would probably not receive institutional review board approval today. At the time of Goldberger's work . . . some of our modern legal and ethical principles had not yet been developed. . . . Conducting research on prisoners was a common procedure."

However, ethical principles from religion and physicians—Hippocrates to Claude Bernard—were available to Goldberger. One basic principle is "never try to harm a patient." Goldberger obviously did not believe that this principle applied to his study. Perhaps he thought that he had consent, that the prisoners were not patients, that the harm would be small, or that there were overriding scientific and social concerns. If Goldberger was convinced that important issues were involved, it should be noted that his studies failed to convince scientists about pellagra ("Skeptics remained unconvinced . . .; These studies . . . were also dismissed . . .").

There is no doubt that this type of experiment in prisoners was common (and remained common—studies like Goldberger's continued for several decades [2] and, in this sense, Goldberger did leave a legacy). But we cannot believe that Goldberger, a hero, followed the crowd willy-nilly and did this type of experiment because everyone else did experiments in prisoners or that because everyone did this type of experiment, it was more acceptable. Finally, it is not as important to speculate about whether an institutional review board today would approve the study but to realize that an institutional review board then probably would have given approval (for example, a review committee in the late 1960s recommended continuing the Tuskegee syphilis study [3]).

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1. **Elmore JG, Feinstein AR.** Joseph Goldberger: an unsung hero of American clinical epidemiology. Ann Intern Med. 1994;121:372-5.
2. **Evans AS.** Further experimental attempts to transmit infectious mononucleosis to man. J Clin Invest. 1950;29:508-12.
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In response: Physicians have always had dilemmas in reconciling our sometimes conflicting obligations to individual persons and society. A major role of informed consent, as used in the past and in many research projects today, is to allow individual persons to volunteer for activities that are aimed mainly at benefiting society (1). Direct benefits for the volunteers can also come from the pardons given to prisoners many years ago for the pellagra experiments or from the money given to participants in experiments at contemporary clinical research centers (1).

Nevertheless, times and customs change, as well as views about ethics. We discussed Joseph Goldberger's scientific achievements during the era in which he lived and worked (2). Evaluators of the past will always be able to find "ethical violations," and reviewers a century from now will doubtlessly note many corresponding flaws in what is being done today. We would like to thank those readers who enjoyed our paper and who were pleased to learn about Goldberger's work but who wrote to us rather than to the Editor.

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