Correspondence

Estrogen-Receptor Polymorphism and Hormone-Replacement Therapy

To the Editor: Often, it is forgotten that the postmenopausal reduction in estrogen levels increases the levels of low-density lipoprotein (LDL) cholesterol and Lp(a) lipoprotein. Sometimes this effect is more important than and precedes the reduction in high-density lipoprotein (HDL) cholesterol levels. Postmenopausal hormonal changes cause a decrease in LDL-receptor activity, with a decrease in the apolipoprotein B–LDL catabolic rate.[1]

This potential effect of estrogens on LDL cholesterol levels is another explanation for the increased rates of heart disease among postmenopausal women. Probably the best explanation is represented by the ratio of LDL to HDL cholesterol or the ratio of total cholesterol to HDL cholesterol.

In their article about estrogen-receptor polymorphisms and the effects of estrogen replacement on HDL cholesterol in women with coronary disease, Herrington et al. (March 28 issue)[2] state, "The numerically greater reductions in levels of LDL cholesterol and apolipoprotein B among women with the IVS1–401 C/C genotype were not sufficiently large to support an inference of interaction," yet they do not provide any information about the ratio of LDL to HDL cholesterol. Would this ratio have supported the inferences of the interaction, if it had been used? And what about the Lp(a) lipoprotein levels?

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1. Arca M, Vega GL, Grundy SM. Hypercholesterolemia in postmenopausal women: metabolic defects and response to low-dose lovastatin. JAMA 1994;271:453-9.
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To the Editor: In his editorial accompanying the article by Herrington et al., Krauss discusses the cardiovascular effects of hormone-replacement therapy.[1] I find the claim that thrombogenic hormones provide a cardiovascular benefit somewhat surprising. I noted elsewhere that more than 60 formulations of 7 progestins and 2 estrogens that could be correlated with clinical side effects had been reported as causing changes in endometrial blood vessels.[2] Arteriolar-wall thickening was reported in women who were receiving such medications and in whom headaches, migraines, hypertension, strokes, or myocardial infarction developed.[2] I would suggest that flawed observational epidemiologic studies with a short median period of hormone use, together with divergent effects of such hormones on lipid metabolism, may have confounded estimates of risk.

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1. Krauss RM. Individualized hormone-replacement therapy? N Engl J Med 2002;346:1017-8.
2. Grant ECG. The Pill, hormone replacement therapy, vascular and mood over-reactivity, and mineral imbalance. J Nutr Environ Med 1998;8:105-16.

The authors reply:

To the Editor: We agree with Dr. Garrido that reductions in the ratio of LDL to HDL cholesterol and levels of Lp(a) lipoprotein are also potentially important effects of hormone therapy. In the Estrogen Replacement and Atherosclerosis trial, we found that among women with the estrogen receptor-α (ER-α) IVS1–401 C/C genotype (i.e., C on both chromosomes in intervening sequence 1 at position 401)

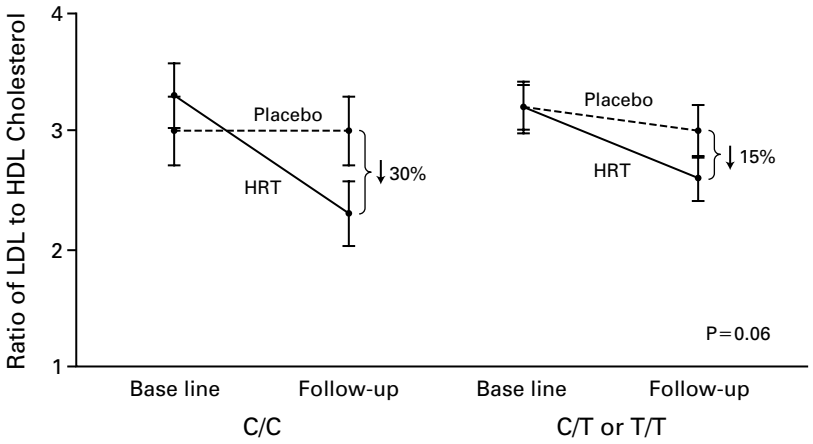

Figure 1. Base-Line and Follow-up Ratios of Low-Density Lipoprotein (LDL) Cholesterol to High-Density Lipoprotein (HDL) Cholesterol among Women Who Received Hormone-Replacement Therapy (HRT) or Placebo, According to the Estrogen Receptor α IVS1–401 Genotype (C/C vs. C/T or T/T).

The bars indicate standard errors. The P value is based on the F test for the interaction between treatment and genotype. IVS1–401 denotes intervening sequence 1 at position 401.

who were treated with hormone therapy, there was a nonsignificant trend toward a greater reduction in the ratio of LDL to HDL cholesterol than among women with the C/T or T/T genotype (Fig. 1).

The reduction in the mean Lp(a) lipoprotein level was also greater in the women with the ER-α IVS1–401 C/C genotype (6.3 percent) than in those with the C/T or T/T genotype (0.5 percent). However, in this case the smaller treatment effects and the wide standard errors do not support a clear differential effect according to the genotype.

On the other hand, we recently reported significantly greater treatment-associated reductions in levels of E-selectin in women with the ER-α IVS1–401 C/C genotype,[1] adding further support for a true drug–gene interaction with respect to several estrogen-sensitive intermediate end points. The effect of this common variant of the gene for ER-α on clinical outcomes is not yet known.

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1. Herrington DM, Howard TD, Brosnihan KB, et al. Common estrogen receptor polymorphism augments effects of hormone replacement therapy on E-selectin but not C-reactive protein. Circulation 2002;105:1879-82.

Development of Kaposi's Sarcoma at the Site of a Biopsy

To the Editor: Dr. Webster-Cyriaque (April 18 issue)[1] reports the development of Kaposi's sarcoma at the site of a recent biopsy of minor salivary glands in a patient with human immunodeficiency virus infection. Although the development of Kaposi's sarcoma at the sites of surgical wounds and other skin trauma (Koebner's phenomenon) has been described before,[2,3] this case is remarkable in that the original biopsy specimen showed no pathological abnormalities or expression of Kaposi's sarcoma–associated herpesvirus, also called human herpesvirus 8 (HHV-8). Immunoperoxidase staining of a specimen from a subsequent biopsy of the Kaposi's sarcoma lesion showed the expression of HHV-8 antigen by macrophages, endothelial cells, and epithelial cells.

Dr. Webster-Cyriaque proposes that the trauma may have precipitated inflammatory changes that recruited HHV-8–infected macrophages to the damaged tissue and induced them to release growth and angiogenic factors. We offer an additional important mechanism for the development of Kaposi's sarcoma in this patient — namely, that hypoxia occurring around the edges of the wound (as a result of the severing of blood vessels) may have activated latent HHV-8 in the infiltrating cells and helped spread the virus to adjacent endothelial or epithelial cells. Our group of investigators has recently found that hypoxia can activate HHV-8 in latently infected B cells,[4] and this may be an important stimulus for the reactivation of HHV-8 in a variety of cells in vivo. Hypoxia-induced activation of HHV-8 may help explain the proclivity for Kaposi's sarcoma to develop at the sites of wounds as well as in the lower extremities, which are often hypoperfused.

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1. Webster-Cyriaque J. Development of Kaposi's sarcoma in a surgical wound. N Engl J Med 2002;346:1207-10.
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Dr. Webster-Cyriaque replies:

To the Editor: Virus was not present at the site of the Kaposi's sarcoma lesion, but there was shedding of HHV-8 into the patient's saliva before the lesion appeared. In this instance, the disease occurred in oral mucosa damaged by a surgical procedure. It is possible that the inflammatory changes associated with wound healing contributed to the recruitment of HHV-8 to the site and the subsequent rapid, aggressive development of the lesion. Since acute exposure of latently infected cells to hypoxia has been found to induce lytic HHV-8 replication, transient hypoxia induced by a surgical incision could have provided a stimulus for HHV-8 reactivation.

It is my opinion that trauma and secondary wound healing, even in the absence of a surgical wound, are key factors in the development of Kaposi's sarcoma. For example, the development of Kaposi's sarcoma in the hallux secondary to trauma has been reported in an immunosuppressed person.[1] In addition, in oral Kaposi's sarcoma, the palate is the most common site of primary involvement, with a particularly high incidence in men who have sex with men.[2] It is possible that palatal trauma occurs in the oral cavity secondary to sexual practices, and it may be the precipitating event, drawing inflammatory cytokines and virus-infected cells to the site. It is also possible that bruising precipitates the lesions detected on the limbs of elderly Mediterranean men who have the classic form of the disease.

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1. Gorsky M, Epstein JB. A case series of acquired immunodeficiency syndrome patients with initial neoplastic diagnoses of intraoral Kaposi's sarcoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:612-7.
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Treatment of Migraine

To the Editor: In their review of the treatment of migraine, Goadsby et al. (Jan. 24 issue)[1] did not mention the importance of caffeine in inducing migraine attacks and thwarting treatment efforts. Variations in caffeine levels, which are inevitable in persons with a substantial intake of caffeine, often induce withdrawal or rebound migraine headaches. The elimination of dietary caffeine frequently results in much greater responsiveness to treatment or even makes long-term pharmacologic intervention unnecessary. Patients and physicians often underestimate caffeine intake by misjudging the volume of large mugs of coffee and big containers of soft drinks.

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1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine — current understanding and treatment. N Engl J Med 2002;346:257-70.

To the Editor: Two additional therapies not mentioned in the review of migraine should be noted because of their tolerability, effectiveness, and low cost. A combination of oral metoclopramide (10 mg) and lysine acetylsalicylate equivalent to aspirin (900 mg) was compared with oral sumatriptan (100 mg) and placebo for the treatment of acute migraine headache in a randomized, controlled trial.[1] Both treatments were superior to placebo, and they had similar efficacy in achieving a reduction from moderate or severe pain to mild pain or none. The group given metoclopramide and lysine acetylsalicylate also had significantly fewer drug reactions and reduced nausea. The assertion by Goadsby et al. that triptans are superior to metoclopramide and aspirin is not supported by these data.

Riboflavin was evaluated for prophylaxis against migraine in a randomized, placebo-controlled trial.[2] Patients with migraine who received vitamin B_2 (400 mg daily) had a significant reduction in the frequency of attacks and in the number of days with headache, and 59 percent of the group receiving riboflavin had at least 50 percent improvement, as compared with 15 percent of the placebo group.

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1. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. Lancet 1995;346:923-6.
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To the Editor: In their review of migraine headaches, Goadsby et al. present various treatment options for both the prevention and the alleviation of acute pain, but they do not mention acupuncture, a treatment without the significant side effects of the medications prescribed for migraine sufferers. Acupuncture has been shown to be effective for both prophylaxis (equipotent to metoprolol[1]) and alleviation of pain.[2] This effect is thought to be due, in part, to an increase in the activity of the opioidergic system.[3]

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1. Hesse J, Mogelvang B, Simonsen H. Acupuncture versus metoprolol in migraine prophylaxis: a randomized trial of trigger point inactivation. J Intern Med 1994;235:451-6.
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To the Editor: As a physician who has migraine headaches, I was struck by the inadequate discussion in the review by Goadsby et al. of the difficulties in managing this common illness. Despite the revolutionary advance associated with the triptans, the authors' data indicate that these drugs are effective in providing sustained freedom from pain in less than 30 percent of patients. Therefore, it is with frustration that I read their comments concerning narcotic analgesia. Although opiates may "mask the pain without suppressing the pathophysiologic mechanism of the attack," this is rarely considered a reason to deny a patient analgesia in medical practice. The statement that opiates may leave "the patient cognitively impaired" is hardly relevant in the case of a severe episode of migraine. Furthermore, I would challenge the statement that the provision of adequate analgesia leads to addiction. Surely this is not true for the majority of patients and will only serve to hinder the provision of symptom relief for millions of patients with this disorder. There is clearly much room for improvement in the management of this disabling disease.

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To the Editor: Goadsby and colleagues present data that I believe are misleading in several respects. First, although the authors say that they have used "therapeutic gain," or the "placebo-subtracted response" (i.e., the response in the treatment group minus the response in the placebo group), in their meta-analysis, this is not the result presented in their figures. A comparison of the data presented in Figures 3 and 4 of their article in the *Journal*[1] with the almost identical data that the authors presented in Figures 1 and 2 of a previous article in the *Lancet*[2] makes it clear that they have presented the overall response rates rather than the placebo-subtracted response rates.

Second, the use of therapeutic gain, or the placebo-subtracted response, as an outcome measure is interesting in itself. I doubt that this statistic has properties appropriate for the use to which the authors have put it. Why do they use it instead of the commonly used odds ratio?

Third, the appropriate comparison clinically is not between the triptans and placebo but between these drugs and other commonly used treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotics, which are cheaper and have been better studied. A discussion restricted to the data for the comparison with placebo is incomplete and misleading.

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1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine — current understanding and treatment. N Engl J Med 2002;346:257-70.
2. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-75.

To the Editor: Botulinum toxin type A appears to be effective, safe, and well tolerated for the treatment of migraine in both double-blind and open-label trials.[1] The mechanisms by which botulinum toxin A exerts its therapeutic effect are the subject of ongoing research. The well-recognized ability of this agent to cause muscle relaxation by inhibiting the release of acetylcholine[2] may not fully explain its benefit in the treatment of migraine. The potential for the inhibition of neuropeptide release, together with acetylcholine, in parasympathetic nerves of the central nervous system might account for the benefit of botulinum toxin A in patients with migraine.

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Editor's note: Dr. Klein is a consultant to Allergan, the manufacturer of Botox.

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The authors reply:

To the Editor: Werner draws attention to one of the many lifestyle manipulations that may be important in migraine — avoidance of excessive caffeine intake. Along with avoiding overuse of analgesic agents, particularly acetaminophen and codeine-containing compounds, avoiding overuse of caffeine is certainly important.

Wyderski discusses treatment with the combination of aspirin and metoclopramide. We agree that this is often a useful approach, and we cited two articles on this strategy (references 62 and 63 in our review). Riboflavin has certainly been shown to be useful as a prophylactic agent in a single controlled study, cited by Wyderski, and we use it from time to time.

The use of acupuncture was not mentioned, as Samuels indicates. The cited study by Hesse et al. did not have a strict placebo group, and the cited study by Vincent had poor case definition. More studies will be required before acupuncture can be deemed clearly effective.[1]

We agree with Barker that migraine can be very difficult to manage, and we concur that even the best class of currently available agents, the triptans, leaves room for improvement. Only a minority of patients with migraine and chronic daily headache are successfully treated with opiates, even in expert hands[2]; we discourage their use. There is a spectrum of manifestations of migraine; treatment-refractory, disabling headache is a problem that requires careful management by headache specialists or neurologists.

In response to Ewart: there is no consensus on the best

strategy for comparing the results of different trials.[3] Use of the rate-ratio approach assumes that the relation between active drug and placebo is multiplicative; the placebo-subtraction approach assumes an additive relation. Both models have advantages and disadvantages. Our article was intended to provide a very broad review of migraine therapy, so we could not present more data on the meta-analysis of triptans. The placebo-subtracted data are presented elsewhere[4]; we used the totality of the data we had to draw our conclusions.

We disagree with Ewart that NSAIDS and narcotics have been better studied than triptans. There are few published data from controlled trials of NSAIDS and triptans; the fullest appeared after our review.[5] There are many methodologic issues in studies comparing triptans with other acute treatments. Unless they are performed by stratifying patients according to clinical need, such studies will not be clinically helpful, because the study populations will be too heterogeneous.

Finally, Klein raises the issue of the use of botulinum toxin type A, citing both open-label studies and a single controlled study. We believe it is premature to conclude that botulinum toxin A will be useful in the treatment of primary headache, and we await data from further controlled trials to establish or refute its role.

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Schistosomiasis

To the Editor: The enormous increase in travel has led to an increase in the number of cases of schistosomiasis in developed countries where the infection is not endemic. Our knowledge of schistosomiasis derives from many studies in countries where it is endemic, as described in the review by Ross et al. (April 18 issue).[1] However, in the new population of nonimmune travelers, the disease has a different clinical pattern. Acute schistosomiasis is practically nonexistent in populations in which the infection is hyperendemic, but it is prominent among returning travelers. In the past three years in our clinic, 23 of 41 patients with schistosomiasis (56 percent) presented at this acute stage. Katayama fever is only one of the manifestations of acute schistosomiasis. The pulmonary manifestations include a prolonged, disturbing, dry cough without fever.[2] Chest radiography may reveal not only interstitial pneumonitis, as mentioned by Ross et al., but also multiple nodules.

The diagnosis of acute schistosomiasis is challenging, since it involves the period soon after exposure and before oviposition occurs. Thus, the standard method of diagnosis — the detection of eggs — is ineffective. Until antigen methods become available, serologic tests should be used to detect schistosomiasis in travelers, since most travelers have not previously been exposed.

Currently, there is no clear policy with regard to treatment of the acute stage. Since much of the pathobiology of schistosomiasis is immunologic in nature,[3] corticosteroids may be effective. Praziquantel, the basic antischistosomal drug used in countries where the infection is endemic, is effective against adult worms but is ineffective against the parasites during the early stage. Artemether, which acts on the juvenile forms of the schistosome,[4] may have a major role in treating the acute stage of infection.

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1. Ross AGP, Bartley BP, Sleigh AC, et al. Schistosomiasis. N Engl J Med 2002;346:1212-20.
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To the Editor: In their excellent review of schistosomiasis, Ross et al. include little information about spinal disease as a cause of neurologic disability in tropical and subtropical areas. Spinal disease most often consists of a mass lesion in the conus medullaris or cauda equina or of arachnoiditis in young children living in areas where schistosomiasis is endemic.[1] Occasional cases occur in travelers and in adults who are seropositive for the human immunodeficiency virus.[2] Clinicians' failure to obtain an appropriate history from travelers and lack of awareness of the entity have resulted in serious delays in diagnosis as well as unnecessary laminectomy in some patients.

Although there are no controlled trials, in my experience praziquantel with or without corticosteroids is effective therapy. The clinical response is often rapid and takes place over a period of several days or weeks. It is not clear why praziquantel is effective, since the spinal lesions are gran-

ulomatous reactions to deposited ova rather than to adult worms. In experimentally infected animals, praziquantel treatment leads to rapid resolution of periovular visceral granulomas. Praziquantel may have ovicidal or antiinflammatory actions as well.[3]

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To the Editor: Women who present with acute appendicitis during pregnancy may have schistosomiasis. In this age of traveling and migration, this possibility must be considered, even in areas where this infection is not endemic. We describe a case of schistosomiasis in a pregnant woman.

A 27-year-old pregnant woman from Somalia was admitted at 22 weeks of gestation because of nausea and a 48-hour history of abdominal pain in the right lower quadrant. The white-cell count was 10,000 per cubic millimeter, without eosinophilia. Acute appendicitis was suspected and was confirmed by laparoscopy and histologic examination. In addition, many schistosomal eggs were seen in the appendiceal wall (Fig. 1). The organism was subsequently identified as *Schistosoma haematobium*. No parasites were found in the stool, urine, or placenta. The postoperative course was uneventful. Three oral doses of praziquantel (20 mg per kilogram of body weight, given 4 hours apart) were administered, and the patient was discharged after 72 hours. She eventually delivered a healthy, full-term female infant.

Parasitic infections during pregnancy are rare, except in some areas where such infections are hyperendemic; in such areas up to 20 percent of pregnant women may be infested with schistosomes.[1] From a pathological point of view, the finding of mucosal and submucosal eggs cannot be considered the cause of appendicitis, because in areas where schistosomiasis is endemic, the parasite is found incidentally at autopsy in 65 percent of appendixes.[2,3] Massive deposition of ova in the appendiceal wall may, however, induce edema, leading to luminal obstruction and ischemia and eventually to necrosis and bacterial infection.[3,4]

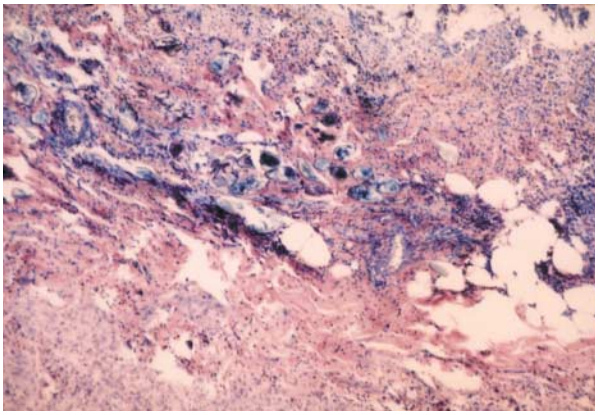

Figure 1. Schistosomal Ova and Marked Eosinophilic Infiltration in the Appendiceal Wall (×200).

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The authors reply:

To the Editor: Schwartz and Rozenman correctly highlight the problem of acute schistosomiasis in returning travelers. Conventional parasitologic diagnostic tests are often not helpful in cases of acute schistosomiasis, so the diagnosis relies on clinical skill and in-depth knowledge. Clearly, the burden of disease resides in the developing world, and some unusual presentations may be anticipated in travelers who are returning from areas where schistosomiasis is endemic. The suggestion that artemether may be useful in the treatment of the acute stage of schistosomal infection has merit, but this approach will require systematic clinical study along lines similar to those described recently by Shuhua et al.[1]

Bhigjee highlights the potential harm that may come to patients as a consequence of clinicians' lack of awareness of the possibility of spinal disease in patients with schistosomiasis. Clinical improvement with praziquantel, with or without corticosteroids, has been reported infrequently but consistently. Further clinical studies will clearly be useful.

Halkic and Gintzburger describe a patient who had an unusual combination of appendicitis and intestinal schistosomiasis during pregnancy and who ultimately had a successful outcome. Although it is tempting to try to find a causal link between two common diagnoses, we urge caution in the attempt to do so. This case does, however, reemphasize the need to be aware of potential complications arising from tropical infectious diseases in immigrants from areas where such diseases are endemic or travelers returning from exotic overseas destinations.

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Nonalcoholic Fatty Liver Disease

To the Editor: In his article on nonalcoholic fatty liver disease (April 18 issue),[1] Angulo reviews extensively the current knowledge about this important condition. Two points, however, merit comment.

First, the role of alcohol consumption is likely to be underestimated as a cofactor in the development of nonalcoholic fatty liver disease. As Angulo states, "a daily intake as low as 20 g [of ethanol] in females and 30 g in males may be sufficient to cause alcohol-induced liver disease." In several of the studies on nonalcoholic fatty liver disease cited in the section on epidemiologic features, excessive alcohol consumption was a criterion for exclusion, but patients with moderate alcohol intake (up to 30 g per day) were included. Excess weight has also been shown to increase the susceptibility to alcoholic liver disease.[2] Since the prevalence of obesity in most series of patients with nonalcoholic fatty liver disease is high (>50 percent),[1] the combination of increased body weight and moderate alcohol intake is likely to enhance the risk of a progressive type of liver disease (involving inflammation and fibrosis).

Second, using data on 54 patients from five series, Angulo calculated that 28 percent had progression of liver damage detected during an average follow-up of 3.5 to 11 years. The statement that the progression from steatosis to steatohepatitis has been recognized must be qualified by the acknowledgment that this progression was observed in subjects with morbid obesity following drastic weight loss after gastroplasty or pronounced dietary restrictions. In the absence of preexisting steatosis or fibrosis, patients with fatty liver of nonalcoholic origin did not have histologic evidence of progression in an earlier study with a follow-up of five years,[3] and this disease was judged to be "an extremely benign condition" in a follow-up study on the natural history of nonalcoholic fatty liver,[4] also cited by Angulo.

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To the Editor: In his review of nonalcoholic fatty liver disease, Angulo briefly mentions several drug therapies tested for use in this condition. One agent, troglitazone, a thiazolidinedione, improved both liver-test results and histologic findings.[1] Paradoxically, troglitazone was removed from the market because of rare, but severe, cases of idiosyncratic hepatocellular injury. Of the currently available thiazolidinediones, rosiglitazone reduces fat content in the liver of subjects with diabetes, as measured by proton nuclear magnetic resonance spectroscopy.[2] These agents improve insulin sensitivity in patients with type 2 diabetes and in those who have insulin resistance but normal glucose tolerance. Some of their action may involve the reduction of intramyocellular and intrahepatic fat, thereby improving insulin sensitivity in these tissues.[3] As a result, body fat may be redistributed to other, less metabolically active storage sites, such as peripheral adipocytes. Since many patients with fatty liver disease have type 2 diabetes, the metabolic syndrome, or both, treatment with thiazolidinediones might be ideally suited for them. The experience with troglitazone has understandably led to reluctance to use these agents in patients with abnormal liver tests, although hepatic toxicity is extraordinarily rare with the currently available thiazolidinediones.[4] To make matters even more complex, however, long-term therapy with thiazolidinediones in obese and diabetic mice results in severe hepatic centrilobular steatosis.[5] This effect may be a reflection of hepatic up-regulation of peroxisome-proliferator–activated receptor γ messenger RNA and receptor protein in these mouse models. Cautious further study is necessary in order to define the precise role and safety of thiazolidinediones in the treatment of nonalcoholic fatty liver disease in patients with insulin-resistant states.

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Editor's note: Dr. Inzucchi has received honorariums from and is a member of the speakers' bureau for Takeda Pharmaceuticals North America and GlaxoSmithKline, manufacturers of thiazolidinediones. Dr. Petersen has received grant support from GlaxoSmithKline. Dr. Shulman has received grant support and honorariums from GlaxoSmithKline.

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To the Editor: Angulo states that patients suspected of having nonalcoholic fatty liver disease should undergo a liver biopsy to confirm the diagnosis and provide prognostic information. In my experience, given the appropriate clinical setting and a negative laboratory and imaging evaluation for other causes of chronic liver disease, the diagnosis of non-

alcoholic fatty liver disease can be made with reasonable accuracy. Although uncommon, the complications of liver biopsy can be very serious and include death.[1] Since there is currently no proven drug treatment for this disease, does the diagnosis have to be confirmed histologically?

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To the Editor: In his review, Angulo did not mention celiac disease. Celiac disease can present with altered liver function and hepatic histologic features indistinguishable from those of nonalcoholic fatty liver disease.[1] Celiac disease is characterized by the presence of chronic intestinal inflammation and altered permeability of intestinal mucosa.[2,3] Celiac disease may represent a possible additional cause of nonalcoholic fatty liver disease, and the finding of altered liver function and the presence of potentially progressive hepatic damage may be the only manifestations.

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Dr. Angulo replies:

To the Editor: The role of alcohol consumption in the development of more advanced liver disease in patients with nonalcoholic fatty liver disease remains controversial. Moderate alcohol consumption has been found to protect against the development of steatohepatitis in severely obese persons.[1] Excess body weight, possibly owing to its common association with steatosis, increases the hepatotoxic effects not only of alcohol, but also of hepatitis C virus and drugs or hepatotoxins. The study by Massarrat et al.[2] cited by Bode included patients who were seen in the 1960s, when it was not possible to rule out other liver diseases that may present with fatty liver. In addition, patients with a daily ethanol intake of up to 70 g were included in that study. Selected patients underwent a second liver biopsy after a mean follow-up of 39 months, which showed periportal and lobular fibrosis in 22.2 percent of patients who had had evidence of simple steatosis in the first liver-biopsy specimen. Hence, although simple steatosis may be associated with a better prognosis within the spectrum of nonalcoholic fatty liver disease, simple steatosis has the potential to progress to steatohepatitis and fibrosis even without drastic weight loss.

Clinical trials evaluating thiazolidinediones in the treatment of nonalcoholic fatty liver disease are currently in progress. Until their results became available, however, the use of thiazolidinediones for the treatment of this liver condition must be restricted to carefully controlled studies.

The clinical diagnosis of nonalcoholic fatty liver disease without biopsy has a positive predictive value of only 59 percent.[3] Given the lack of effective medical therapy for all patients with nonalcoholic fatty liver disease, a liver biopsy may not be necessary for the simple purpose of making the diagnosis in a patient with clear risk factors for this condition. But liver biopsy may provide the most valuable diagnostic information in patients who do not have risk factors for nonalcoholic fatty liver disease, as well as in patients who do not have improved liver-test results after weight loss and appropriate metabolic control. Factors that can help to identify patients in whom liver biopsy may provide the most useful prognostic information were discussed in my article.

Liver biopsy in most patients with celiac disease who present with elevated aminotransferase levels shows nonspecific reactive hepatitis. In a few cases, liver biopsy shows fatty liver, but steatosis is predominantly microvesicular, in contrast to the predominantly macrovesicular steatosis found in patients with nonalcoholic fatty liver disease. In addition, other features, such as predominant portal or periportal inflammation or fibrosis, hemosiderosis, and intrahepatic cholestasis, are found in patients with celiac disease and fatty liver but are rarely seen in patients with nonalcoholic fatty liver disease.[4,5] Celiac disease is not a cause of nonalcoholic fatty liver disease.[6]

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Mechanical Extraction of a Basilar-Artery Embolus with the Use of Flow Reversal and a Microbasket

To the Editor: Local intraarterial fibrinolysis has improved the outcome for patients with acute vertebrobasilar occlusion. The procedure has increased survival rates to 30

to 45 percent[1-3] and resulted in rates of recanalization ranging from 50 to 75 percent.[2-5] However, thrombolysis can also lead to intracerebral hematomas, even in the posterior circulation (incidence, 0 to 15 percent),[1-5] as well as to systemic hemorrhage.

Mechanical extraction of embolic material offers a potential alternative to fibrinolysis, especially for patients in whom fibrinolysis is contraindicated or in whom it has failed. We and others have tested several extraction devices experimentally. Recently, with the approval of our local ethics committee, we used such a device (Neuronet, Guidant) in a multicenter, phase 1 study — the Neuronet Evaluation in Embolic Stroke Disease study — after testing it in a flow model and in animals. The micro-guide-wire–based device has a self-expanding basket that can be pushed through a standard microcatheter and used to retract an embolus. However, two attempts to retract an embolus in each of two patients with acute occlusion of the distal basilar artery failed, and the patients then underwent fibrinolysis. We subsequently altered the technique for embolus retraction by controlling the blood flow. We could reverse the flow in the vertebrobasilar system by using balloons in the vertebral or subclavian arteries or by using catheters adapted to the diameters of the vertebral arteries.

We report on the use of the combined technique of flow control and embolus retraction in a 17-year-old girl who had a previously unidentified patent foramen ovale and asymptomatic venous thrombosis. She had a progressive brainstem stroke, with headache and bilateral tinnitus, that began 10 hours before she was enrolled in the study. Five hours after the onset of symptoms, hemihypesthesia developed on the left side, as well as vertigo, double vision, and somnolence. Three hours before angiography, hemiplegia, anarthria, spontaneous nystagmus, and bilateral ptosis developed. Progressive loss of consciousness led to coma two hours before treatment (score on the National Institutes of Health stroke scale, 24; score on the Glasgow coma scale, 4). Computed tomography showed no hypodensity but a hyperdense basilar artery, and cerebral angiography showed that the middle section and top of the basilar artery were occluded by an embolus. The posterior cerebral arteries were supplied collaterally from the circle of Willis. We transiently occluded both vertebral arteries with soft silicone balloons (in the left vertebral artery, next to the coaxial catheter), while retracting the embolus with the extraction device through the coaxial catheter in the left vertebral artery. The clot was retrieved from the basilar artery, but part of the embolus fell through the basket into the intracranial segment of the left vertebral artery. The remaining thrombotic material was removed by suction through the 6-French coaxial catheter, and it was identified as a fresh red thrombus by histologic analysis. Complete recanalization of the vertebrobasilar system was achieved (Fig. 1). The patient recovered quickly and was asymptomatic one day later (diffusion-weighted magnetic resonance imaging showed only a hyperintense dot of about 2 mm in the pons).

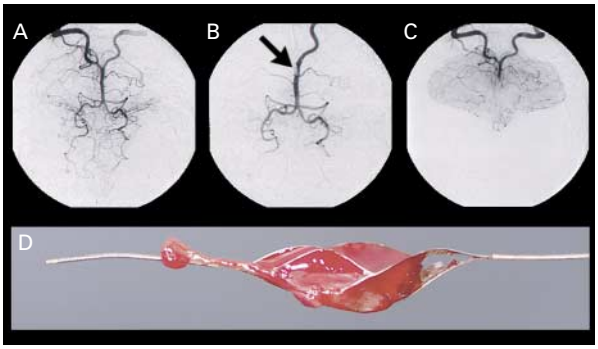

Figure 1. Removal of an Embolus from a 17-Year-Old Girl Who Had Progressive Stroke, with Hemiplegia, Anarthria, Bilateral Ptosis, and Loss of Consciousness.

Angiography of the left vertebral artery shows an embolism in the midbasilar and distal basilar artery (Panel A). The embolus was retrieved from the tip of the basilar artery with the extraction device, which is shown in the left vertebral artery (arrow in Panel B). The flow to the basilar artery was then reestablished through the right vertebral artery with the deflation of the balloon in that artery. The left vertebral artery remained blocked (by a balloon beside the catheter) to hold the thrombus in place. Complete recanalization was achieved (Panel C) after suction of the remaining thrombotic material into the coaxial catheter and deflation of the balloon in the left vertebral artery. Panel D shows the extraction device with the thrombus. Histologic analysis showed that the thrombus was composed of 60 percent erythrocytes, 25 percent thrombocytes, and 15 percent granulocytes.

On the basis of preliminary experience with various mechanical devices for the recanalization of intracranial arteries, we recommend using flow control to support the extraction of a thromboembolus (which the proximal flow otherwise keeps in place like a floating cork), as well as to protect distal branches from fragments of the embolus.

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