

1. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365-70.
2. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2005;23:4347-53.

## The Lessons of Vioxx

**TO THE EDITOR:** With regard to the Perspective article by Representative Waxman (June 23 issue),<sup>1</sup> Merck initiated the Vioxx Gastrointestinal Outcomes Research (VIGOR) study to evaluate the gastrointestinal safety of Vioxx as compared with naproxen and sought a change in the Food and Drug Administration (FDA) label on the basis of its results. The cardiovascular results of this study were widely discussed on television, in newspapers, and in medical journals. Until the FDA label change, and consistent with Merck's long-standing policies, Merck instructed its sales force not to initiate discussions about VIGOR but to submit physicians' questions about the cardiovascular profile of Vioxx to Merck's Medical Services department. The staff of this department provided detailed information about VIGOR and the cardiovascular safety of Vioxx in response to more than 100,000 physicians' requests.

Waxman also selectively describes the training of Merck's professional representatives and the materials provided to physicians. Our representatives were instructed to present a balanced description of the risks and benefits of Vioxx that were fully consistent with the FDA-approved label and our understanding of the cardiovascular risks associated with Vioxx.

Most important, Waxman fails to provide the context of Merck's marketing efforts — Merck's belief in the safety profile of Vioxx and its benefits. Merck's marketing of Vioxx was informed by all available clinical and scientific data. The data available at the time of VIGOR entailed the combined analysis of randomized, controlled clinical trials involving more than 28,000 patients that showed no increased cardiovascular risk with Vioxx as compared with placebo or nonsteroidal antiinflammatory drugs (NSAIDs) other than naproxen.

It is largely as a result of Merck's postmarketing studies of Vioxx — including the Adenomatous Polyp Prevention on Vioxx trial that led to our voluntary withdrawal of the drug — and our commu-

nication of the results that we informed an important scientific discussion regarding the risks and benefits of the entire class of medications. This discussion has led the FDA to conclude that all NSAIDs may present cardiovascular risks. That is the lesson learned from Vioxx. In considering broader FDA policy issues, neither Congress nor the American public should be led astray by misleading characterizations of Merck's activities or of the underlying science.

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1. Waxman HA. The lessons of Vioxx — drug safety and sales. *N Engl J Med* 2005;352:2576-8.

**REPRESENTATIVE WAXMAN REPLIES:** Frazier argues that Merck's instructions to sales representatives for talking to doctors about Vioxx were "consistent with Merck's long-standing policies." Yet he does not explain why these policies permitted mention of Vioxx's gastrointestinal benefits in the VIGOR study but not of its cardiovascular risks.

Frazier defends Merck's flawed cardiovascular analysis of preapproval studies, which was mailed to thousands of physicians and featured in marketing materials, as "fully consistent with the FDA-approved label." In fact, the analysis was not mentioned on the label and actually was rejected by the FDA for inclusion in the label.<sup>1</sup> An FDA official told Congress that Merck's depiction of Vioxx as safer than the alternatives was "scientifically inappropriate" and "ridiculous."<sup>2</sup>

Merck deserves credit for conducting additional studies. But while those studies were ongoing, the company did not fairly present available evidence to doctors. It is telling that the company still relies on its 28,000-patient meta-analysis. In February 2001, the FDA found this analysis to have "serious methodological limitations."<sup>3</sup>

Drug advertisements for consumers are receiv-

ing increased scrutiny. The lesson of Vioxx is that industry marketing to physicians deserves attention too.

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1. Labeling negotiations between Merck Research Laboratories and Food and Drug Administration. Telecon minutes. February 8,

2002. (Accessed September 8, 2005, at <http://www.democrats.reform.house.gov/features/vioxx/Tab1.pdf>.)

2. Waxman HA. The marketing of Vioxx to physicians: memo to Democratic members of the Government Reform Committee. May 5, 2005. (Accessed September 8, 2005, at <http://democrats.reform.house.gov/story.asp?ID=848>.)

3. Arthritis Advisory Committee, Food and Drug Administration. Vioxx (rofecoxib, Merck). February 8, 2001 (meeting transcript). (Accessed September 8, 2005, at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2.rtf>.)

## Medical Mystery: Abdominal Pain — The Answer

**TO THE EDITOR:** The Medical Mystery in the August 4 issue<sup>1</sup> involved a 40-year-old man who presented with a four-day history of pain in the left upper quadrant of the abdomen, accompanied by fatigue, fever, sweating, and sore throat. A computed tomographic scan was obtained; it revealed multiple splenic infarcts (Fig. 1) due to acute infectious mononucleosis. Laboratory studies on admission showed an elevated white-cell count (13,800 per cubic millimeter) with 51 percent lymphocytes, 31 percent of which were atypical, as well as the following abnormal liver-function values: aspartate aminotransferase, 123 U per liter; alanine aminotransferase, 244 U per liter; alkaline phosphatase, 216 U per liter; and total bilirubin, 0.9 mg per deciliter (15.4  $\mu$ mol per liter). Transthoracic echocardiography revealed no abnormalities, and blood cultures showed no growth. An initial monospot test was negative, as were serologic studies for cytomegalovirus and hepatitis A, B, and C viruses. At a follow-up visit with a primary care physician one week later, a repeated monospot test was positive, and a polymerase-chain-reaction analysis for Epstein–Barr virus DNA from the previous week was found to be positive.

Persons with acute infectious mononucleosis, often called “the kissing disease” because of its spread among adolescents by salivary contact, typically present with the triad of exudative pharyngitis, lymphadenopathy, and splenomegaly; splenic rupture or splenic infarction is a possible complication. The monospot test detects heterophil antibodies that are present in 90 percent of patients with acute infectious mononucleosis, but the test may require up to three weeks to become positive.

Primary infection with the Epstein–Barr virus in older persons is often associated with liver-func-



**Figure 1. Computed Tomographic Scan of the Abdomen.**  
The arrow indicates an area of splenic infarction.

tion abnormalities. The patient in the current case may have contracted the infection from a new sex partner within the past 10 months. His liver-function values normalized over the next few months, and he had a full recovery.

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*Editor's note:* We received 1030 responses to this Medical Mystery from 73 countries. Forty-six percent of the respondents, many of whom specifically noted the splenic infarct, correctly identified acute Epstein–Barr virus infection. Twenty-eight percent correctly identified a splenic infarct but