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THE AUTHORS REPLY: We appreciate Dr. Seutin's close reading of our review. We agree that the physiologic roles of 5-hydroxytryptamine type 3 channels remain unclear. Adding to the complexity in this area, recent data indicate that, depending on the agent, inhaled anesthetics can enhance or inhibit the function of 5-hydroxytryptamine type 3A receptors.¹ The effects of inhaled anesthetics on channels that conduct background potassium-leak currents are also fascinating, complex, and difficult to summarize briefly. The findings of Patel et al.² and others do not suggest that the various background potassium channels have a common role in anesthetic actions. A reasonable inference is that they may influence the side-effect profiles of different agents. In revising and condensing Table 2, we truncated the entry for NMDA-sensitive glutamate channels, which should read, "Cation conductance for

calcium and magnesium inhibition." The entry for α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and kainate should read, "Cation conductance for calcium," which is subunit-dependent.³

It has been brought to our attention that the structure of sevoflurane shown in Figure 1 is erroneous. The formula for the correct structure is $\text{CH}(\text{CF}_3)_2\text{-O-CH}_2\text{F}$. To our embarrassment, the structures for methoxyflurane ($\text{CH}_3\text{-O-CF}_2\text{-CHCl}_2$) and enflurane ($\text{CHF}_2\text{-O-CF}_2\text{-CHFCl}$) are also incorrect. Regarding nitrous oxide, some sources suggest that the oxygen atom is bound to both nitrogen atoms in a cyclic triangle, but in fact the arrangement is linear. The structure is best represented as a resonant hybrid of $\text{N}\equiv\text{N}^+\text{-O}^-$ and $\text{N}^=\text{N}^+=\text{O}$.

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Breast-Cancer Genomics

TO THE EDITOR: In Figure 1 of their article, Wooster and Weber (June 5 issue)¹ ignore an important paradox by dismissing mutations in the ATM (ataxia-telangiectasia mutated) gene as not contributing to breast cancer. Current theories propose that ATM senses DNA damage and then signals BRCA1. For example, ATM phosphorylates BRCA1, signaling it to arrest the cell cycle after DNA damage due to ionizing radiation. Pathogenic BRCA1 mutations markedly increase the risk of breast cancer. The dependence of BRCA1 on ATM thus makes it logical that mutations in the ATM gene would also increase the risk of breast cancer. Similarly, mutations in the CHEK2 gene increase the risk of breast cancer, and CHEK2 may have functional links with ATM.^{2,3} The authors accept the idea of a "BRCA3" gene with little

hesitation, although such a gene has not yet been identified. ATM could actually represent BRCA3, according to claims that heterozygotes for ATM mutations may account for up to 20 percent of cases of breast cancer. Stipulations to these claims are required because of data that do not support the presence of excess truncating ATM mutations in early-onset breast cancer.⁴ However, a clearer discussion of at least the proposed relations among ATM, CHEK2, and BRCA1 would facilitate clinical application and help resolve this confusing paradox.

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TO THE EDITOR: I take exception to Wooster and Weber's statement that "among mutation carriers, this procedure [prophylactic mastectomy or prophylactic oophorectomy] has been shown to reduce the risk of breast and ovarian cancer by more than 60 percent and 95 percent, respectively." Although it has been well documented that prophylactic mastectomy does not result in the removal of all breast tissue,¹ ovarian cancer cannot develop in women who undergo prophylactic oophorectomy, with the very rare exception of cases in which some ovarian tissue is inadvertently left in situ because of unrecognized adherence of a portion of the ovary to the pelvic sidewall. What does happen in a small percentage of women who undergo prophylactic oophorectomy is the subsequent development of papillary serous carcinoma of the peritoneum, which is a diffuse involvement of the lining of the peritoneal surfaces with a carcinoma identical to papillary serous carcinoma of the ovary and in which there is no demonstrable primary ovarian carcinoma.² This distinction is important because women who undergo prophylactic oophorectomy still need postoperative surveillance for the possible development of papillary serous carcinoma of the peritoneum.

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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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THE AUTHORS REPLY: In response to Dr. Piver, we agree that papillary serous carcinoma of the peritoneum is a more accurate term than ovarian cancer to describe the disseminated intraperitoneal cancer that can occur after prophylactic oophorectomy. However, this clinical entity is indistinguishable in presentation and prognosis from the stage III pap-

illary serous ovarian carcinoma that can occur in women with intact ovaries. The source of papillary serous carcinoma of the peritoneum remains unknown, but regardless of its origin, it most commonly appears as disseminated intraperitoneal disease, and almost never as a resectable tumor mass. In our own series of 259 carriers of BRCA1 and BRCA2 mutations who underwent prophylactic oophorectomy, 2 patients (0.7 percent) received a diagnosis of papillary serous carcinoma of the peritoneum after a mean follow-up of 10.7 years.¹ Thus, given the low incidence of this carcinoma after prophylactic oophorectomy in the highest-risk population studied to date, and given the absence of data showing that the outcome of this carcinoma can be altered by surveillance, it is difficult to make a case for screening women at high risk for papillary serous carcinoma of the peritoneum after prophylactic oophorectomy.

In response to Dr. Friedenson, we agree that ATM mutations have a plausible role in heritable susceptibility to breast cancer. A number of findings — the function of ATM in response to DNA damage, susceptibility to breast cancer in association with genetic mutations in this pathway, the segregation of ATM mutations in a few families with breast cancer, the excess rate of breast cancer in female family members of ATM homozygotes, and findings in a recently developed murine model — all support this hypothesis.^{2,3} However, as we stated, these data remain controversial because of conflicting reports³ and because of the absence of specific ATM sequence variants that are consistently associated with a significantly increased risk of breast cancer. Thus, at present, we believe that ATM is best represented within the approximately 50 percent of genes associated with breast-cancer susceptibility that remain unidentified or uncharacterized.

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