

emphasized by Dr. Aiken, was addressed as a secondary end point in our trial. The analysis showed that the addition of chemotherapy to standard radiation therapy had no significant detrimental effect on the quality of life.<sup>1</sup>

Dr. Seiter suggests that salvage therapy could explain why there was no difference in progression-free survival in the two groups we studied. Indeed, 72 percent of the patients initially treated with radiation therapy alone received salvage chemotherapy with an alkylating agent. Actually, more than 60 percent of patients received temozolomide after progression.

Dr. Ashby and colleagues believe that carmustine-impregnated wafers should be recognized as an alternative treatment. In our opinion, the results with carmustine wafers were disappointing, particularly because all patients had to undergo debulking surgery to implant the wafer to the resection cavity.<sup>2</sup> Patients with glioblastoma receiving carmustine wafers had a median survival of 13.5 months, as compared with 11.4 months with placebo, with no significant difference in survival beyond 18 months. In the European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada trial, patients who underwent surgery had a median survival of 12.9 months with initial radiation therapy, as compared with 15.8 months for patients who received treatment with temozolomide during and after radiation therapy ( $P < 0.001$ ). More important, our trial shows an improvement in the two-year survival rate, which we consider meaningful. Malignant glioma is a disease of the brain beyond the visible local extension. Thus, treatments that target only local disease have inherent limitations. There may be a rationale for future trials that combine treatment with carmustine wafers and temozolomide with radiation therapy. The local administration of carmustine could be a strategy to exhaust the MGMT reservoir of the tumor.

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**DR. DEANGELIS REPLIES:** In the study by Stupp et al., the addition of temozolomide to radiotherapy prolonged the median survival by 2.5 months and increased the 2-year survival rate from 10.4 percent to 26.5 percent. Dr. Aiken says this is old news and an insignificant improvement. However, recent data indicate that many patients with glioblastoma in the United States receive suboptimal standard care; only 54 percent of patients receive adjuvant chemotherapy, regardless of whether they are treated in the community or at an academic institution.<sup>1</sup> Temozolomide is easy to add, has acceptable side effects, and could benefit, although not cure, thousands of patients. Many have called for a new way to treat glioblastoma, but to date, signal-transduction inhibitors, small molecules, and immunotherapy have been disappointing and have not yet led to even the incremental change observed with the addition of the relatively nontoxic temozolomide.<sup>2,3</sup> The study by Stupp et al. and the companion tissue analysis by Hegi et al. suggest that glioblastoma is a tractable problem. This will stimulate further research as investigators realize that we are starting to see the forest — and not just the trees.

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## Euthanasia in Severely Ill Newborns

**TO THE EDITOR:** Verhagen and Sauer (March 10 issue)<sup>1</sup> emphasize that euthanasia is becoming acceptable medical practice for infants in the Nether-

lands in whom hopeless and unbearable suffering is present. Doctors are not all-knowing, but pediatric palliative care is a dynamic process that remedi-

ates suffering in children through careful assessment and treatment of all symptoms; the quality of life is enhanced, and families are supported.<sup>2</sup>

Access to pediatric palliation is poor, even in countries with first-class medical systems. A study in the Netherlands<sup>3</sup> revealed that the youngest patient receiving palliative care between March 2001 and February 2002 was seven years old. Verhagen and Sauer's conviction that life-ending measures can be acceptable in newborns conflicts with the recommendations Sauer made on behalf of the Confederation of European Specialists in Paediatrics. He and his colleagues invoked the doctrine of double effect and stated that every form of intentional killing should be rejected in pediatrics.<sup>4</sup> Perhaps if he and his patients had better access to palliative care, he might return to his ethical stance of 2001.

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**TO THE EDITOR:** Verhagen and Sauer observe that all reported cases of euthanasia in newborns in the Netherlands involved infants with severe forms of spina bifida. Mandatory folic acid fortification of flour would have prevented the development of spina bifida in most of these infants. The failure of the Dutch government and that of many other countries to require folic acid fortification remains a tragic policy error.<sup>1</sup> When will European and other governments require this simple, safe, and inexpensive action? Folic acid fortification has been shown in several countries not only to prevent spina bifida, but also virtually to eliminate folate-deficiency anemia and to reduce serum concentrations of homocysteine, with likely reductions in deaths from strokes and heart attacks.<sup>2-4</sup> I encourage all physicians to advocate forcefully for their governments

to require folic acid fortification, using the emergency powers and expedited, short review process provided for in public health regulations. These regulations should be invoked to prevent the severe disease and disability that will continue to occur unnecessarily until mandatory folic acid fortification is implemented.

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**TO THE EDITOR:** When my cousin Jay was born, the doctors said, in so many words, that his diagnosis and prognosis were certain: severe spina bifida, a very poor quality of life, and no hope of improvement.<sup>1</sup> Jay did suffer. He suffered 26 surgeries and all of the indignities that follow from paralysis, incontinence, and bodily disfigurement. Moreover, like the rest of us, Jay never became fully self-sufficient.

Yet Jay bore his suffering with irrepressible hope and good humor that inspired and encouraged innumerable people who had the privilege of knowing him. When he died three days before his 14th birthday, 2000 people attended the funeral to celebrate Jay's uncommonly rich life. A passerby commented, "Someone important must have died."

With different parents, Jay could have qualified for the Groningen protocol. Doctors might have "performed a deliberate life-ending procedure"<sup>1</sup> in Jay after making claims no mortal can sustain<sup>2</sup> — that his prognosis was "certain," and his suffering was "hopeless and unbearable."<sup>1</sup> Those of us who knew Jay are glad there was no such opportunity.

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**DRS. VERHAGEN AND SAUER REPLY:** We agree with Oakley that folic acid fortification is important. However, it cannot prevent all abnormalities in newborns that cause unbearable suffering.

We cannot comment on Jay's case, described by Curlin, because we did not know him. He suffered, but according to Curlin, the suffering was acceptable. As we noted in our Perspective article, the role of the parents is paramount. Clearly, these parents were supportive, but the question is whether, without these parents, would the suffering have been bearable?

Murphy and Pritchard raise the issue that pediatric palliative care is not always accessible or adequate. They suggest that improvement in palliative care services could lead to a situation in which euthanasia in sick newborns would no longer be practiced. We agree that patients will certainly profit from improved access to palliative care. At the same time, we are convinced that euthanasia in patients with a hopeless prognosis and severe and sustained

suffering, waiting for the "ideal" standard of care, can be acceptable. The Groningen protocol was designed to motivate physicians to adhere to the highest standards of decision making and to reduce hidden euthanasia by facilitating reporting. The protocol requires that all possible palliative measures be exhausted before euthanasia is performed. This requirement might do more in mobilizing the availability of palliative care services than the current situation of unreported practice.

The recommendations that Murphy and Pritchard refer to are a consensus statement of pediatricians in Europe.<sup>1</sup> Sauer's personal view is that active life-ending procedures can be acceptable.

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## Medical Mystery — The Answer

**TO THE EDITOR:** The medical mystery in the April 7 issue<sup>1</sup> involved a radiograph (Fig. 1) in a patient who had undergone four lifesaving procedures between 1949 and 2002. The radiograph shows remnants of a therapeutic pneumothorax for pulmonary tuberculosis, a coronary-artery bypass graft, a stent repair of a type B aortic dissection, and a dual-chamber pacemaker for complete atrioventricular block.

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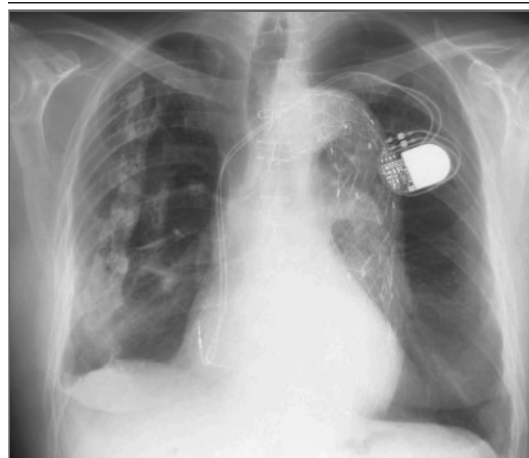
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*Editor's note:* We received 729 responses to this medical mystery, from 68 countries. This is an underestimate of the actual number of people participating, since many responses represent a collaborative effort; for example, one response represented the collective effort of the University of Alabama internal-medicine residents, from their morning report.

Thirty-nine percent of the respondents correctly identified the old right-sided lung collapse used as a treatment for tuberculosis, 64 percent identified median sternotomy for a coronary-artery bypass graft, 77 percent identified the placement of a descending aortic stent, and 93 percent identified the placement of a pacemaker. The group from the University of Alabama was among the 25 percent of respondents who correctly identified all four proce-



**Figure 1.** Radiograph in a Patient Who Underwent Four Lifesaving Procedures between 1949 and 2002.

dures. Another 40 percent identified three of the four procedures correctly. Other suggested procedures included mastectomy, aortoaxillary bifemoral graft, esophageal repair, and lung transplantation.

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