

## CORRESPONDENCE


**ADDITIONAL CORRECTIONS: INTERFERON FOR HEMANGIOMAS OF INFANCY**

To the Editor: Inaccuracies in our paper "Interferon Alfa-2a Therapy for Life-Threatening Hemangiomas of Infancy"<sup>1</sup> prompted a careful review. On the basis of our reanalysis and an interim review by a standing faculty committee of the Harvard Medical School, we submitted a revised Table 1, published as a correction notice.<sup>2</sup> The final review of this committee concluded that ambiguities in method, presentation, and conclusions should be clarified and that errors remained that should be corrected.

In our original description of the assessment of outcomes, we never stated that lesions were measured; however, the use of the terms "dimensions" in the Methods section and "percentages" in the Methods section and the table could have implied a quantitative method. It is not possible to quantify precisely the tumors we were describing, because of their heterogeneity in size, shape, and anatomical location. Therefore, the Methods section should have read: "Premature regression was defined as an obvious decrease of 50 percent or more in the *size* [not *dimensions*] of the hemangioma." We estimated the percent change by comparing pretreatment photographs, radiographs, or endoscopic examinations with those obtained after treatment; the assessment was adjusted according to clinical status for most patients. We used the combination of methods appropriate for each patient but did not weight the contributions of each method formally. For example, in Patient 2, who had Kasabach-Merritt syndrome, 70 percent regression was estimated subjectively on the basis of the reduction in the size of the lesion as shown by photography, the

diminished turgor of the lesion, and reversal of coagulopathy. In Patient 14, 60 percent regression was estimated subjectively on the basis of the 100 percent regression of the airway lesion shown by endoscopy and magnetic resonance imaging (MRI), modified because of residual mediastinal disease (seen on MRI) and the patient's clinical status. For clarification, we now include a table showing the methods used to estimate the response in each patient (Table 1).

In all patients, the period of assessment began at the start of interferon treatment. In the Methods section of our paper, we stated incorrectly, "Premature regression . . . was sustained for at least six months during treatment or after the withdrawal of the medication."<sup>1</sup> To clarify: Patients 8, 16, 19, and 20 required less than 6 months of treatment; they were assessed at 3 months, 3 months, 4 months, and 5.25 months, respectively. Follow-up procedures were not performed if they required general anesthesia and were not clinically indicated — i.e., MRI was not performed for Patients 4 and 20, and endoscopy was not performed for Patient 8. Clinical assessments alone were used, in these instances, to document sustained regression.

We also stated incorrectly in the Methods section, "To be eligible for the study, infants had to have a life-threatening or vision-threatening hemangioma that failed to respond to a two-week course of corticosteroid therapy. . . ." Therapeutic doses of corticosteroids were given before interferon therapy to 15 patients, for one month during interferon therapy to Patient 1, and for seven weeks during interferon therapy to Patient 12.<sup>2</sup> Patient 1 died and Patient 12's hemangioma grew while she was receiving both drugs. Patients 3 and 14 began receiving interferon after 12 days of corticosteroids, not 14 days, because of their worsening conditions. Interferon alone was given to Patients 10, 13, and 16.<sup>2</sup> In 15 patients for whom corticosteroids failed, interferon was initiated during the period when the dose of corticosteroid was being tapered, since it was not considered safe to discontinue the latter abruptly.

We stated incorrectly in the Methods section, "A complete blood count and tests of hepatic . . . function were performed monthly." We were unable to obtain monthly laboratory studies for 18 patients; therefore, we cannot reach any conclusions about toxic effects. We must add to the record,

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Table 1. Methods Used to Assess Outcomes of Interferon Alfa Treatment.\*

CONDITION AND PATIENT NO.	PHOTOGRAPHY	MRI	CT	US	ENDOSCOPY	HEM	CLINICAL STATUS
Coagulopathy							
1	X					X	X
2	X					X	X
3	X					X	X
4		X				X	X
Cervicofacial							
5	X						X
6			X		X		X
7	X						X
8					X		X
9		X					X
10	X						X
11	X						X
12	X						X
13		X					X
14		X			X		X
Periorbital							
15	X						X
16	X						X
17	X						X
Visceral							
18		X					X
19				X			X
20		X					

\*CT denotes computed tomography, US ultrasonography, and HEM the evaluation of coagulopathy. Clinical status denotes the turgor and color in Patients 1, 2, 3, 10, 11, 15, and 16; the airway opening in Patients 5, 6, 7, 8, 9, 10, 13, and 14; improved cardiac status in Patients 6, 12, 18, and 19; and decreased ulceration in Patients 7 and 17. Patient 13 was originally given a diagnosis of hemangioma on the basis of MRI; the oral lesions improved, whereas the skin lesions persisted, and a biopsy of the latter showed venous malformation (January 1993).

however, that four patients, not one, had transient neutropenia, and eight patients had liver aminotransferase levels two to five times their pretreatment levels. Patient 15 was hyperactive for one day after receiving a gradually escalated dose of interferon to 6 million units per square meter of body-surface area. Furthermore, Patient 14 missed 13 doses of interferon during six months of therapy.

We are embarrassed by our errors and regret them. We apologize to the readers for any misunderstanding and thank our colleagues for their assistance in correcting our report.

ALAN EZEKOWITZ, M.B., CH.B., D.PHIL.  
JOHN MULLIKEN, M.D.  
JUDAH FOLKMAN, M.D.  
Children's Hospital

Boston, MA 02115

1. Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *N Engl J Med* 1992;326:1456-63.
2. Correction to: Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *N Engl J Med* 1994;330:300.

#### ADJUVANT CHEMOTHERAPY IN BREAST CANCER

*To the Editor:* Bonadonna et al. (April 6 issue)<sup>1</sup> addressed the effect of drug-induced amenorrhea on the outcomes of 78 premenopausal patients treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) (Table 2 of the article). In 50 patients who had drug-induced amenorrhea and in 28 patients who did not, the rates of 20-year relapse-free survival were 39 percent and 30 percent, respectively. The authors concluded that there was no significant difference in relapse-free survival between these two groups. We estimated the hazard ratio for relapse-free survival between women with drug-induced amenorrhea and those without it from 10 published studies. The hazard ratio ranged from 0.39 to 0.86, with a median of 0.56. Therefore, if we assume that drug-

induced amenorrhea is associated with a 40 percent reduction in the rate of relapse, the analysis carried out by Bonadonna et al. in 78 patients had a power lower than 40 percent.

The authors' statement that "drug-induced amenorrhea is not an important predictor of response" contradicts almost all published studies and is not supported by their own data — which, incidentally, show a 22 percent reduction in the risk of relapse at 20 years. Nine of 10 published studies, some of them large,<sup>2-5</sup> reported longer periods of relapse-free survival in patients with drug-induced amenorrhea than in those without it. The difference was statistically significant in eight studies. In one of these studies, the prognostic role of drug-induced amenorrhea was also confirmed in terms of overall survival.<sup>4</sup>

Although these findings do not necessarily imply that the main effect of chemotherapy in premenopausal patients is due to chemical castration, they do indicate that the predictive role of drug-induced amenorrhea should not be denied.

LUCIA DEL MASTRO, M.D.  
MASSIMO COSTANTINI, M.D.

Istituto Nazionale per la  
Ricerca sul Cancro  
16132 Genoa, Italy

ANGELO RAFFAELE BIANCO, M.D.  
University of Naples Medical School  
80131 Naples, Italy

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2. Bianco AR, Del Mastro L, Gallo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. *Br J Cancer* 1991;63:799-803.
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4. Tormey DC, Gray R, Abeloff MD, et al. Adjuvant therapy with a doxorubicin regimen and long-term tamoxifen in premenopausal breast cancer patients: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1992;10:1848-56.
5. Ludwig Breast Cancer Study Group. A randomized trial of adjuvant combination chemotherapy with or without prednisone in premenopausal breast cancer patients with metastases in one to three axillary lymph nodes. *Cancer Res* 1985;45:4454-9.

*To the Editor:* The article by Bonadonna and colleagues is a welcome addition, since it involves a relatively long follow-up. I was confused, however, by two things in this article. The authors state that "48 of 179 patients in the control group were disease-free at 20 years," yet only 44 of 179 patients in the control group were even alive at 20 years. Also, the authors discuss the "ease of administration and the virtual absence of severe acute toxicity" in relation to the chemotherapy regimen administered, yet only 42 of the 207 patients in the chemotherapy group received at least 85 percent of the planned dosages.

MICHAEL D. NEWMAN, M.D.  
Clinton Memorial Hospital  
Wilmington, OH 45177

*To the Editor:* In his editorial on breast-sparing surgery for breast cancer (April 6 issue),<sup>1</sup> Henderson says, "Local failure is a particularly difficult consequence of therapy for most patients because it is readily apparent and is thus a constant reminder that the tumor is no longer curable." This is incorrect. In 1991, the National Surgical Adjuvant Breast and Bowel Project concluded that local failure is curable, saying that "local recurrence is a marker of risk for, not a cause of, distant metastases."<sup>2</sup> Besides the studies cited by Henderson, other studies with 10 years of follow-up have supported this conclu-

sion.<sup>3,4</sup> No reliable data support a contrary conclusion. In the study by Jacobson et al. (also in the April 6 issue),<sup>5</sup> recurrent disease confined to the ipsilateral breast developed in 19 patients, who were treated with salvage mastectomy. The projected rate of disease-free survival at 10 years is 67 percent. This is not significantly different from that of all the women initially treated with lumpectomy and radiation therapy. I found no data in Stablein's reanalysis of National Surgical Adjuvant Breast and Bowel Project Protocol B-06 suggesting that lumpectomy compromised survival.<sup>6</sup> But that trial did not record the size of each recurrent tumor. Clearly, a recurrent tumor that exceeds the size of the primary lesion becomes an added survival threat. How does Henderson conclude that local failure is incurable?

RICHARD A. EVANS, M.D.  
Houston, TX 77057-2015  
1011 Augusta Dr.

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2. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumor recurrence after lumpectomy. *Lancet* 1991;338:327-31.
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5. Jacobson JA, Danforth DN, Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995;332:907-11.
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The authors reply:

*To the Editor:* Del Mastro et al. attempt to reintroduce the concept of a "prognostic" role for drug-induced amenorrhea following adjuvant chemotherapy in premenopausal women. Amenorrhea depends on the patient's age and the total dose of alkylating agents. Before this side effect begins, patients are at risk for relapse while still menstruating. There are a few techniques for taking this problem into account. In our medical records we reported the date of the last menstrual period for every patient; we therefore used a time-dependent model to analyze our data.<sup>1</sup> Although we had a limited number of patients, in this model the relative risk of relapse for women in whom amenorrhea developed was 0.87 (95 percent confidence interval, 0.48 to 1.51;  $P=0.65$ ). We emphasize that in contrast to other studies in which amenorrhea was found to be a favorable prognostic factor, our protocol involved CMF chemotherapy alone — that is, without the addition of tamoxifen, prednisone, or fluoxymesterone (Halotestin).<sup>2,3</sup>

To answer Dr. Newman: we made clear in the Methods section, as well as at the bottom of Table 1, that in the analysis of relapse-free survival second malignant conditions other than contralateral breast cancer and deaths due to other causes were not considered events. At 20 years, 125 of the 179 patients in the control group have died of progressive breast cancer, 10 have died of other causes, 6 are alive with breast cancer, and 38 are alive and free of disease. Adjuvant CMF chemotherapy was indeed easy to administer, it was always given on an outpatient basis, and it was devoid of life-threatening toxicity. Acute hematologic and nonhematologic toxic effects were always mild to moderate and reversible. We have detailed the reasons why only a minority of our patients received the optimal dose of CMF<sup>4</sup> — among them, that drug doses were calculated on the basis of ideal rather than actual body surface, that low starting doses of chemotherapy were used in women over 60 years of age, that some patients refused to complete the planned treatment cycles

for psychological reasons, and that doses were adjusted downward to avert side effects.

GIANNI BONADONNA, M.D.  
PINUCCIA VALAGUSSA, B.S.  
Istituto Nazionale per lo Studio  
e la Cura dei Tumori

20133 Milan, Italy

1. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
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*To the Editor:* Dr. Evans contests the point that a local or regional recurrence in skin, lymph nodes, or muscle has the same prognostic effect on survival as recurrence at a distant site. I believe that confusion regarding this point, as with so many other issues of contention concerning breast cancer, arises from the relation between treatment and outcome. It is true that some patients with local recurrences have long survival times after treatment with surgery, radiotherapy, or both; the duration of survival can be decades. This is also true for some patients with distant recurrences. The critical questions are whether there is a relation between the treatment and the survival and whether any patient with recurrent disease is "curable."

There is marked variation in the behavior of breast cancers. The disease may recur within a few months or up to 40 years after the first treatment. Similarly, survival after recurrence may vary from a few months to several decades. Therefore, an individual physician may treat a few patients who do well by chance alone and conclude that the treatment causes the good outcome. However, such claims based on a small number of patients have been refuted by properly controlled trials. It is in this context that the observations on the use of screening mammography followed by mastectomy and those on mastectomy or radiotherapy or both followed by adjuvant systemic therapy are so remarkable. No other interventions have been demonstrated to prolong survival to the same degree. Certainly there are no similar data for the treatment of recurrent breast cancer, including local recurrences.

A new cancer found entirely within the breast after radiotherapy does not appear to behave like a local recurrence, but rather like a new cancer in the contralateral breast after mastectomy. If the new cancer is of the same stage or a lower one than the original cancer, the patient's prognosis remains largely unchanged.<sup>1</sup>

I. CRAIG HENDERSON, M.D.  
University of California,  
San Francisco, CA 94143

1. Harris JR, Recht A, Amalric R, et al. Time course and prognosis of local recurrence following primary radiation therapy for early breast cancer. *J Clin Oncol* 1984;2:37-41.

#### DEFERIPRONE IN IRON OVERLOAD

*To the Editor:* Olivieri et al. (April 6 issue)<sup>1</sup> are to be congratulated on their work on deferiprone, which, in addition to demonstrating the drug's efficacy in iron chelation, is the only study so far to have addressed some of the controversies surrounding the use of the drug.<sup>2-5</sup>

Our experience with autoimmune phenomena has not been

confined to just one case of fatal drug-induced systemic lupus erythematosus.<sup>2</sup> We have found a significantly higher incidence of antinuclear antibodies in patients with thalassemia treated with deferiprone (7 of 27) than in those not receiving the drug (2 of 63,  $P < 0.01$ ). Antibodies to histones were detected in four of the seven patients with antinuclear antibodies who were receiving deferiprone and in neither of the two not receiving the drug.<sup>6</sup> In one patient, both types of autoantibodies had disappeared five months after the discontinuation of treatment with deferiprone, and in another patient, who had no antibodies to histones, antinuclear antibodies had disappeared four months after the discontinuation of treatment.<sup>6</sup>

The disparity between our findings in Indian patients<sup>4,6</sup> and those in the patients described by Olivieri et al. is striking. Deferiprone is an orphan drug that has to be manufactured locally for each group investigating it. Is it possible that a difference in the manufacturing process or final formulation of the drug accounts for the difference in the adverse reactions? This issue needs to be addressed, because deferiprone has recently been made commercially available for routine use in India. Careful post-marketing surveillance is essential, especially on the part of the Indian regulatory authorities, because in India the package insert for deferiprone does not recommend immunologic investigations in the case of joint problems.

Sutton, Surrey SM2 5PT,  
United Kingdom

J. MEHTA, M.D.  
S. SINGHAL, M.D.  
Royal Marsden Hospital

Bombay 400 056, India

B.C. MEHTA, F.R.C.P., D.Sc.  
Nanavati Hospital

1. Olivieri NF, Brittenham GM, Matsui D, et al. Iron-chelation therapy with oral deferiprone in patients with thalassemia major. *N Engl J Med* 1995;332:918-22.
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*To the Editor:* Oral deferiprone is a potentially important agent in the treatment of iron overload in patients with thalassemia, but the toxic effects of the drug require further investigation before it is recommended for general use. Deferiprone had minimal side effects in the trial by Olivieri et al.; none of the 21 patients had neutropenia, and only 1 reported joint pain. A multicenter trial from India, however, reported that substantial proportions of the patients had joint pain (28.8 percent) and minor gastrointestinal problems (20 percent); neutropenia occurred in three patients (2.1 percent).<sup>1</sup> Similar findings were reported by Kontoghiorghes.<sup>2</sup>

In a trial of oral deferiprone in 20 patients with thalassemia, my colleagues and I observed a rapid initial decrease in the serum ferritin level within 3 months after the start of therapy (from  $3355 \pm 1611$  to  $1746 \pm 1044$  ng per milliliter), followed by a gradual decrease (from  $1746 \pm 1044$  to  $1251 \pm 1011$  ng per milliliter) over the next 12 months.<sup>3</sup> Gastrointestinal problems developed in 30 percent of the patients, joint pain in 30 percent, and neutropenia in one patient (5 percent). We have studied the response pattern for only 15 months. It is

possible that shorter cycles of deferiprone therapy, rather than continuous administration, can improve compliance and reduce the incidence of toxic effects.

DEBASIS ADHIKARI, M.B., B.S.

Memorial Sloan-Kettering  
Cancer Center  
New York, NY 10021

1. Agarwal MB, Adhikari D, Marwaha RK, Gogtay JA. Multicentre clinical studies with the oral iron chelator (deferiprone, L-1:Cipla Ltd) in transfusion dependent thalassaemia — the Indian experience. Presented at the Sixth International Conference on Oral Chelation in the Treatment of Thalassaemia and Other Diseases, Nijmegen, the Netherlands, January 27 and 28, 1995. abstract.
2. Kontoghiorghes GJ. Update of worldwide iron chelation therapy with L-1 (Deferiprone). Presented at the Sixth International Conference on Oral Chelation in the Treatment of Thalassaemia and Other Diseases, Nijmegen, the Netherlands, January 27 and 28, 1995. abstract.
3. Adhikari D, Basu Roy T, Chandra S, Adhikari SK. Analysis of fall in serum ferritin after chelation of iron with deferiprone (L-1) in  $\beta$  thalassaemia and haemoglobin E  $\beta$  thalassaemia. *Curr Sci* 1995;68:839-40.

*To the Editor:* Nathan's editorial on deferiprone (April 6 issue)<sup>1</sup> refers to the use of the drug in a "London hospital without sufficient studies of toxic effects in animals and without Hider's approval." These studies were carried out at the Royal Free Hospital with the approval of both the Department of Health and the Royal Free Ethical Committee.<sup>2,3</sup> These phase 1 trials laid the foundation for all subsequent clinical studies of deferiprone throughout the world. The clinical side effects of idiosyncratic agranulocytosis, arthropathy, zinc deficiency, and nausea were all first described in these London studies and have recently been reviewed.<sup>4,5</sup> The side effects of deferoxamine, like those of deferiprone, could not have been reliably predicted from animal studies.

Nathan states that the frequency of agranulocytosis and arthropathy associated with deferiprone is not yet known. A substantial literature, based on observations in several hundred patients, reports on both these phenomena.<sup>4,5</sup> The incidence of agranulocytosis has been estimated at 1.6 percent, and the incidence of less severe neutropenia at 2.4 percent. The incidence of joint symptoms has ranged from 0 to 38.5 percent among trials, with an overall incidence of 18 percent. The incidence of these side effects may well depend on the age, sex, and ethnic group of the patients; the type of bone marrow disease; the patients' iron status; the dose of deferiprone given; and the period of exposure to the drug.<sup>6</sup>

Nathan also states that deferiprone does not readily reduce excessive body iron stores "below a certain level." This is also true of deferoxamine; in patients with thalassemia major receiving long-term treatment with deferoxamine, iron stores are 5 to 10 times larger than normal.

Nathan asks whether enough is known about the pharmacologic properties of deferiprone. More studies could be undertaken, but there are already several detailed reports that have recently been reviewed.<sup>7</sup> He suggests that deferiprone, like desferithiocin, may cause renal side effects. However, no such effects have been reported in any of the patients receiving long-term treatment with deferiprone. Finally, Nathan questions whether adolescents will swallow enough of the oral chelator to allow its appropriate use. Olivieri et al. have clearly shown that compliance with deferiprone therapy is far superior to that with deferoxamine.

It is clear that not all patients will be able to tolerate deferiprone. The side effects of nausea, arthropathy, and neutropenia or agranulocytosis have caused patients in all trials to discontinue the drug. Nevertheless, for about 75 percent of the

patients in large studies, long-term compliance has been excellent, and the drug is potentially life-saving for patients who cannot afford deferoxamine or comply with the required regimen or who are allergic to the drug.

A.V. HOFFBRAND, D.M., D.SC.  
B. WONKE, M.D.

London NW3 2QG,  
United Kingdom

Royal Free Hospital  
School of Medicine

1. Nathan DG. An orally active iron chelator. *N Engl J Med* 1995;332:953-4.
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Dr. Nathan replies:

*To the Editor:* Though Drs. Hoffbrand and Wonke believe that the incidence of myelotoxicity associated with deferiprone therapy is 2 percent, we really do not know what the incidence is. It is certainly no more than 10 percent; how close the actual incidence is to 2 percent or 10 percent will be known in the fullness of time, when the larger study by Olivieri et al., now in progress, has been completed.

I do not agree with Hoffbrand and Wonke's comments about deferoxamine and iron stores. The toxicity of deferoxamine is largely due to its capacity to deplete iron even when iron stores are already low, which is why deafness and other serious central nervous system effects can occur if the dose of deferoxamine is not lowered as iron stores fall.

I did not suggest that deferiprone would cause renal toxicity. I used desferithiocin as an example of an active oral iron chelator that was a disappointment.

In my editorial, I stated that deferiprone is as important an option as marrow transplantation. But we just do not have enough experience with the drug to know whether it will provide protection from heart disease in the long term. I am concerned that the rapid clearance of deferiprone from the blood after an oral dose has been administered will leave the heart unprotected. We need better kinetic studies of iron and the drug if we are to understand the risks and benefits.

Finally, readers might have noted an inadvertent but important error in the editorial (a correction notice was published in the May 11 issue).<sup>1</sup> On page 953, in line 25 of the right-hand column, the text should have read "when the concentration of the drug in body fluids," not "when the concentration of iron in body fluids."

DAVID G. NATHAN, M.D.  
Children's Hospital

Boston, MA 02115

1. Correction to: An orally active iron chelator. *N Engl J Med* 1995;332:1315.

#### PROTECTION AGAINST TETANUS

*To the Editor:* The serologic survey by Gergen et al. (March 23 issue)<sup>1</sup> corroborates earlier studies showing that more than half of Americans over the age of 50 lack what are considered protective levels (>0.15 IU per milliliter) of tetanus antitoxin.

Although serologic surveys often predict the epidemiologic features of a disease, the incidence of tetanus is far better predicted by a history of inadequate primary immunization with tetanus toxoid. Almost all cases occur in persons who never completed a primary immunization series, did not receive appropriate treatment of a wound, or both.<sup>2</sup>

There is strong epidemiologic evidence that primary immunization confers a long-term benefit even though levels of antitoxin wane with time. Among the few patients who contract tetanus but report having completed a primary immunization series, the disease is milder than in less well immunized persons. Booster doses of tetanus toxoid induce anamnestic increases in antitoxin levels even after intervals of 25 to 30 years. Experimental studies in animals and humans indicate that low antitoxin titers still provide substantial protection.

High rates of seronegativity for antitoxin indicate poor compliance with the current recommendation of the Advisory Committee on Immunization Practices that booster doses of tetanus toxoid be given every 10 years.<sup>2</sup> Despite this serologic evidence of widespread susceptibility among adults, tetanus is rare among those who have received a complete primary series. The epidemiologic evidence indicates that routine decennial boosters are of marginal value and are not cost effective.<sup>3</sup> In addition, brachial-plexus neuropathy, which the Institute of Medicine has accepted as causally related to tetanus toxoid (with 0.5 to 1 case per 100,000 recipients of tetanus toxoid),<sup>4</sup> has occurred almost exclusively in adults who have received multiple injections of tetanus toxoid.

As an alternative strategy to the policy of giving decennial booster immunizations, the Task Force on Adult Immunization of the American College of Physicians recommends that "special emphasis be given to the completion of a primary immunization series with tetanus and diphtheria toxoids, followed by a single booster at the age of 50 for persons who have completed the full pediatric series, including the teenage and young-adult booster."<sup>5</sup> The task force believes that recommending the booster dose at this specific age will result in better compliance and raise the levels of immunity to tetanus and diphtheria in adults. Both the Task Force on Adult Immunization and the Advisory Committee on Immunization Practices strongly recommend the age of 50 as an ideal time to review immunization status and other preventive health measures (e.g., cancer screening, diet, and estrogen replacement). In addition to an evaluation of immunity to tetanus and diphtheria, an assessment should be made of risk factors that would indicate a need for pneumococcal vaccine, annual influenza immunization, or both.

PIERCE GARDNER, M.D.  
State University of New York  
at Stony Brook  
School of Medicine

Stony Brook, NY 11794

F. MARC LAFORCE, M.D.  
Genesee Hospital

Rochester, NY 14607

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