Correspondence

Chemotherapy in the Elderly

To the Editor: Sargent et al. (Oct. 11 issue)[1] report that adjuvant chemotherapy with fluorouracil is as effective in older patients with resected colon cancer as it is in younger patients. Their conclusion is based on the absence of a statistically significant interaction between age and treatment effect for both overall and disease-free survival. However, the survival curves for treated and untreated patients who were more than 70 years old seem closer than the curves for treated and untreated younger patients. In our opinion, the absolute gain in survival is the measure that should be discussed with patients when deciding whether to use an adjuvant treatment. We suspect that the absolute differences in the study by Sargent et al. were small, and we would like to know what the absolute gain in survival was at each year of follow-up.

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1. Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091-7.

To the Editor: Sargent et al. conclude that "it is reasonable to consider chemotherapy in nearly all patients with resected stage II and stage III colon cancer." But the idea that adjuvant therapy is beneficial for patients with stage II colon cancer is not supported by the data. Patients with stage II disease and those with stage III disease do not have the same rate of survival at five years. Indeed, the rate of overall survival among patients with stage II disease may be as high as 78 percent, and elderly patients included in a trial may have rates of overall survival that exceed those in an age- and sex-matched population of persons without cancer.[1,2]

The flaws of the studies on which the authors base their meta-analysis are in part responsible for this conclusion, since many of the studies have grouped patients with stage II disease and those with stage III disease together, as if the characteristics of the two stages were similar. The conclusion that adjuvant therapy can be safely given to elderly persons is welcome news for patients with stage III disease. To advocate such treatment for patients with stage II disease is to include a large group of patients who have a high rate of survival with surgery alone, exposing particularly those who are elderly only to the side effects of the treatment, not to the survival benefit.

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To the Editor: Sargent et al. state that elderly persons receive adjuvant chemotherapy less frequently than younger patients, citing rates of chemotherapy use from a study that linked 1992 data from the Surveillance, Epidemiology, and End Results (SEER) Program with Medicare data for 1992.[1] However, two more recent studies of SEER–Medicare data report rates of use of adjuvant chemotherapy among elderly persons with stage III colon cancer that are considerably higher than the rates reported by Sargent et al.[2,3]

With the use of data from 1992 to 1996, these studies showed that the rate of adjuvant-chemotherapy use was

higher than 73 percent among persons who were 65 to 69 years old and was higher than 68 percent among those who were 70 to 74. According to one of these studies, by 1996, the rate of adjuvant-chemotherapy use was 81 percent among persons who were 65 to 74 years old.[2] This rate is about 70 percent higher than that reported by Sargent et al. An analysis of adjuvant-treatment rates based on medical records for persons of all ages who received a diagnosis of stage III colon cancer in 1990, 1991, or 1995 showed that the rate of use of fluorouracil was 74 percent among persons under the age of 55 years, 71 percent among those who were 55 to 64 years old, and 67 percent among those who were 65 to 74 years old (Potosky A, National Cancer Institute: personal communication).

The more recent estimates should be used as the benchmark for chemotherapy use in the elderly. In addition, rates of adjuvant-chemotherapy use for persons who are 65 to 74 years old do not appear to be markedly lower than those for persons who are 55 to 64. These findings suggest that age may not greatly influence clinicians' decisions about treatment for "young old" persons with stage III colon cancer.

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2. Schrag D, Cramer LD, Bach PB, Begg CB. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst 2001;93:850-7.
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The authors reply:

To the Editor: Perrone et al. have requested the absolute differences between survival rates among treated and untreated patients, according to the age group. Because there was no interaction between age and treatment, we believe that the data we initially presented — the five-year survival rates of 71 percent for treated patients and 64 percent for untreated patients — represent the most appropriate and reliable measure of the absolute benefit for both age groups (≤70 years and >70 years). As shown in Table 1, the age-specific rates for each year of follow-up are very similar for the two age groups in terms of the absolute benefit of treatment; among patients who were 70 years of age or younger, the rate of overall survival at five years was 71 percent for treated patients, as compared with 64 percent for untreated patients; among those over the age of 70, the five-year rates of overall survival were 69 percent for treated patients and 62 percent for untreated patients.

We agree with Nauta that the benefit of adjuvant treatment for patients with stage II cancer is controversial, with different groups of investigators drawing different conclusions.[1,2] Our intention was to honor the initial randomization used in each study included in our pooled analysis; each of these studies included both patients with stage II disease and those with stage III disease in the initial randomization. In the community, adjuvant treatment of patients with stage II cancer is common, with 31 percent of Medicare-age patients who have stage II disease receiving adjuvant therapy.[3] We support the current U.S. intergroup strategy of mounting separate trials for stage II disease and for stage III disease. In addition, stratification of patients into high-risk and low-risk groups on the basis of molecular markers such as microsatellite instability may eventually prove to be a clinically useful decision-making tool.

TABLE 1. OVERALL SURVIVAL ACCORDING TO AGE AND YEAR OF FOLLOW-UP.

YEAR OF FOLLOW-UP	AGE, >70 YR		AGE, ≤70 YR	
	TREATED	UNTREATED	TREATED	UNTREATED
	percent of patients			
1	93	92	96	95
2	85	84	88	85
3	79	76	81	76
4	72	68	76	69
5	69	62	71	64

Regarding the frequency of chemotherapy in patients with stage III cancer who are 65 to 74 years old, it is indeed promising news that the use of therapy in such patients is increasing, as Warren and Brown note. However, both reports that they cite[4,5] conclude that age continues to be a strong predictor of chemotherapy use and that further efforts are needed to ensure that elderly patients and their physicians have full information and receive appropriate treatment.

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1. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol 1999;17:1349-55.
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Tuberculosis and Treatment with Infliximab

To the Editor: In support of the findings of Keane et al. (Oct. 11 issue),[1] we describe the reactivation of latent tu-

berculosis in a 19-year-old Pakistani man treated with infliximab for sight-threatening uveitis of unknown cause despite extensive investigation. The patient presented with a 3-week history of fever, sweats, dry cough, and breathlessness 60 days after the first of three intravenous boluses of infliximab at a dose of 5 mg per kilogram of body weight. Upper and midzone interstitial lung shadowing and extensive lymphadenopathy were noted on computed tomographic scanning. Lymph-node biopsy revealed heavy infiltration with acid-fast bacilli. The patient's symptoms improved after the initiation of treatment with rifampin, pyrazinamide, and isoniazid, but his temperature continued to spike (39.5°C) for a further six weeks. Immune-function testing demonstrated that his T cells were able to make interferon-γ in response to stimulation with purified protein derivative. No other immunodeficiency was noted.

Twenty months earlier, the patient had been screened according to the guidelines of the British Thoracic Society[2] as a close contact of a patient with smear-positive pulmonary tuberculosis and deemed not to be infected. A grade 2 response to a Heaf test at the time was thought to be consistent with prior bacille Calmette–Guérin vaccination. The timing of events, extent of disease, and clinical course described are all consistent with an association between infliximab and the reactivation of tuberculosis.

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To the Editor: Keane et al. reported that active tuberculosis may develop soon after the initiation of treatment with infliximab. We describe a case of disseminated histoplasmosis after similar treatment.

A 19-year-old man had Crohn's disease (diagnosed at the age of 12 years) that was not controlled by conventional treatment. While still receiving mercaptopurine he was given infliximab (5 mg per kilogram) in June 2000. Symptoms of Crohn's disease improved, and a second dose of infliximab was given in September 2000. Three weeks later he presented with fever (temperature, 40.0°C), followed over the next four weeks by a nonproductive cough, abdominal discomfort, watery stools, and massive hepatosplenomegaly, with progressive leukopenia (cell count, 2.31×10^9 per liter) and thrombocytopenia (cell count, 79×10^9 per liter). A workup revealed no evidence of active Crohn's disease, a malignant condition, tuberculosis, or infection with Epstein–Barr virus, cytomegalovirus, or bacteria. Histopathological examination of biopsy specimens of the colon, liver, and bone marrow showed noncaseating granulomas. Fungus-like organisms were detected within the granulomas, and cultures were positive for *Histoplasma capsulatum*. Therapy with amphotericin B (15 mg per kilogram) was administered, followed by itraconazole (200 mg per day). The patient recovered uneventfully.

The patient had grown up in Louisiana and had attended college in Ohio, areas where histoplasmosis is endemic. This fact and the short interval between the infliximab infusion and the appearance of symptoms suggest that our patient had a reactivation of prior infection.

Tumor necrosis factor α (TNF-α) is an important immune modulator, and neutralization of this cytokine significantly suppresses the immune response. Inhibition of TNF-α resulted in delayed clearance of *Pneumocystis carinii* in the lungs of immunocompetent mice.[1] Blockade of TNF-α exacerbated chronic infection in CD4+ cell–depleted mice. In addition to neutralizing secreted TNF-α, infliximab exerts an immunosuppressive effect by attacking immune effector cells that express membrane-bound TNF-α,[2] further impairing host defenses.

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To the Editor: Keane et al. report that tuberculosis developed in some patients with Crohn's disease or rheumatoid arthritis after treatment with infliximab. We believe that these patients need to be described separately, especially with respect to their clinical characteristics and the interval between infliximab treatment and the appearance of tuberculosis. There is a possibility that some patients who have been given a diagnosis of Crohn's disease actually have abdominal tuberculosis. Both conditions can present with transmural spread and penetration through the muscle coat, although this presentation is relatively less common in Crohn's disease. These conditions have a similar microscopic appearance that includes granulomas, and the caseation that is characteristic of tuberculosis is often difficult to identify.[1] In areas where abdominal tuberculosis is more frequent, some criteria must be fulfilled to differentiate intestinal tuberculosis from Crohn's disease: there must be histologic evidence of tubercles with caseation necrosis; there must be a good typical gross description of operative findings, with biopsy of mesenteric nodes showing histologic evidence of tuberculosis; inoculation into animals or culture of the suspected tissue must result in the growth of tubercle bacilli; and histologic examination must show *Mycobacterium tuberculosis* in a lesion.[2] In an urban British population with a large number of Asian immigrants, abdominal tuberculosis was not infrequent, whereas Crohn's disease occurred rarely in Asian immigrants.[3] A clear distinction in describing the general characteristics of patients with Crohn's disease and rheumatoid arthritis in whom tuberculosis developed will be useful, given that when we diag-

nose Crohn's disease we are at risk of underdiagnosing abdominal tuberculosis.

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To the Editor: Keane et al. describe the occurrence of active tuberculosis soon after the initiation of treatment with infliximab. We describe a nine-year-old girl with classic systemic-onset juvenile idiopathic arthritis,[1] who was given a diagnosis of osteoarticular tuberculosis shortly after commencing treatment with etanercept. She had been treated with corticosteroids (initially intravenous methylprednisolone, then oral corticosteroids) and methotrexate. However, owing to poor control of the disease, etanercept (0.4 mg per kilogram) was substituted for methotrexate, with a good response initially (the active-joint count and levels of acute-phase reactants were decreased and her sense of well-being improved). Five weeks later, a painful swollen left ankle developed, but the patient remained well and afebrile. Clear synovial fluid was aspirated from the joint (which was sterile on routine culture). Etanercept was recommenced, and she remained well. However, three weeks later *M. tuberculosis* complex was isolated, and its identity was confirmed by a gene probe; it then was found to be a fully sensitive strain of *M. tuberculosis.* An isotopic bone scan revealed additional sites of presumed infection, but the chest radiograph was normal. Tracing of the patient's contacts identified no source of infection. Etanercept was stopped. Antituberculosis treatment included standard triple therapy, extended for 12 months, with rifampin and isoniazid continued as maintenance therapy, since the reactivation of systemic juvenile idiopathic arthritis necessitated the resumption of methotrexate therapy. She continues to take corticosteroids (<0.5 mg per kilogram every other day), and 18 months later, she is well and her arthritis is clinically inactive.

Osteoarticular tuberculosis is uncommon in children in Britain. Tuberculosis should be considered in immunocompromised patients, especially those with monoarthropathy, and in patients who have received anti-TNF therapy, since such therapy may suppress the classic signs of infection.

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To the Editor: Study of animal models has provided a guide to the safety of the inhibition of TNF in humans, including its effect on susceptibility to tuberculosis.[1,2] The report by Keane and colleagues highlights important safety concerns regarding the reactivation of tuberculosis in recipients of TNF inhibitors, but we found that the absence of TNF had no adverse effect on morbidity or overall survival in TNF-deficient mice that had not previously been exposed to *M. tuberculosis.*

We conducted a prospective age- and sex-matched 30-month study of morbidity and mortality in a cohort of 106 wild-type C57BL/6 mice and 98 C57BL/6 mice rendered TNF-deficient by gene targeting (Riminton DS, et al., unpublished data). The cohorts were divided into two groups: one housed under pathogen-free conditions and the other under conventional conditions. Survival of TNF-deficient mice was equivalent to that of controls ($P=0.9$ by the log-rank test; hazard ratio, 1.02; 95 percent confidence interval, 0.66 to 1.6), irrespective of environmental variations. The same TNF-deficient mice, however, had greatly increased susceptibility to disease on inhalational challenge with virulent *M. tuberculosis.*[2]

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2. Bean AG, Roach DR, Briscoe H, et al. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol Mycobacterium tuberculosis infection, which is not compensated for by lymphotoxin. J Immunol 1999;162:3504-11.

The authors reply:

To the Editor: The findings of Lim et al. support our finding of an association between infliximab and tuberculosis. Since our report was published, the Food and Drug Administration (FDA) has received 47 additional reports of infliximab-associated tuberculosis, for a total of 117 cases through November 30, 2001. Given that the amount of underreporting is unknown, the estimated rate of tuberculosis reported to the FDA for the first year of treatment with infliximab is approximately 41 per 100,000 in U.S. patients with rheumatoid arthritis, 9 per 100,000 in U.S. patients with Crohn's disease, and 224 per 100,000 in all non-U.S. patients with rheumatoid arthritis or Crohn's disease. The infliximab package insert states that screening for and treatment of latent tuberculosis are indicated before the drug is prescribed.[1] This precaution is important because cases of tuberculosis influence public health as well as the health of the patient. Our data do not rule out an association between etanercept and tuberculosis, and the case re-

ported by Myers et al. highlights the need for continued surveillance for tuberculosis with the use of all anti-TNF agents.

The case reported by Zhang et al. of histoplasmosis in association with infliximab emphasizes the possibility that infections that are dormant in granulomas may become susceptible to reactivation when TNF is neutralized. Of the 11 cases of histoplasmosis after infliximab that have been reported to the FDA, 10 required care in the intensive care unit and 1 was fatal. This experience highlights the importance of the early diagnosis and treatment of histoplasmosis.

We acknowledge the difficulty in differentiating Crohn's disease from enteric tuberculosis, as mentioned by De Rosa et al. Indeed, mycobacterial infection has been suggested as a possible etiologic agent of Crohn's disease.[2] To date, 27 cases of tuberculosis have been reported in patients with Crohn's disease after treatment with infliximab for a median of 10 weeks (range, 4 to 52). Sixteen of these patients had extrapulmonary disease, and five had disseminated tuberculosis. In our study, one patient who was initially considered to have Crohn's disease was reclassified as having enteric tuberculosis and was excluded from the analysis. Available data suggest that these cases of tuberculosis were not from an otherwise high-risk group, such as inner-city Asian immigrants. The possibility of occasional mistaken diagnoses does not detract from the importance of testing for tuberculosis infection in patients with Crohn's disease before the initiation of infliximab therapy.

The immunologic events that explain the possible link between blockade of TNF and the failure of granuloma to contain bacilli are poorly understood. We have seen an interferon-γ–independent mycobactericidal effect of macrophages that is mediated by host-cell apoptosis and dependent on TNF.[3] Consistent with this finding is the report of Lim et al. that the secretion of IFN-γ by T cells was normal after stimulation with purified protein derivative in their patient who was receiving infliximab. Bean et al. have demonstrated normal T-cell activation in tuberculosis-infected mice that have a disruption of the TNF gene.[4] Given the pleiotropic nature of TNF, it most likely influences many aspects of the immune response to tuberculosis.

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Lack of Health Insurance and Overall Health

To the Editor: Baker et al. (Oct. 11 issue)[1] used disability data from the 1992 and 1996 surveys of the Health and Retirement Study to assess the effect of health insurance status on the risk of the development of a physical disability. Unfortunately, as pointed out in the article, the wording of the questions related to disability on the Health and Retirement Study surveys changed between 1992 and 1996.

The initial survey, in 1992, inquired about the performance of physical tasks. The wording was, "How difficult is it for you to [perform this task]?" and the potential answers were "not at all difficult," "a little difficult," "somewhat difficult," "very difficult," and "something you can't do at all." In 1994, subjects were asked about the same tasks, but the question was changed to, "Do you have any difficulty with [this task]?" Subjects who reported difficulty were asked, "Is that a little or a lot of difficulty?" In 1996, the question was changed again and became, "Because of a health problem do you have any difficulty with [this task]?" The responses ("yes," "no," "can't do," or "don't do") were recorded for the same tasks as in the previous surveys.

To deal with these changes in format, Baker et al. restricted their analyses to participants who reported a new disability in 1996. They made the assumption that participants who answered "not at all difficult" in 1992 and then either "yes" or "can't do" in 1996 had a new disability. We examined the effect the wording change may have had on the outcome by using an experimental module from the 1994 survey in which 771 subjects were asked questions about disability in both the 1992 and the 1994 formats. Since the first part of the 1994 question format is almost identical to the 1996 format, we were able to compare the participants' responses to the old (1992) and new (1996) questions.

We used the algorithm described by Baker et al. to determine the number of participants in whom a new mobility- or agility-related disability would appear to have developed solely on the basis of the change in the question (Table 1). We found that 14 percent of the subjects would appear to have a new agility-related disability but that only 4 percent would appear to have a new mobility-related disability. Baker et al. reported that 17.1 percent of the continuously insured participants and 28.8 percent of the continuously uninsured participants had a new disability related to mobility ($P<0.001$) and that 32.2 percent and 38.7 percent, respectively, had a new agility-related disability ($P=0.003$). The lack of concordance with the results from the

TABLE 1. PARTICIPANTS WHO REPORTED A NEW DISABILITY IN MOBILITY OR AGILITY IN 1994 AS A RESULT OF THE CHANGE IN QUESTION FORMAT.

NEW DISABILITY	MOBILITY	AGILITY
	no. (%)	
No	663 (95.7)	617 (85.9)
Yes	30 (4.3)	101 (14.1)
Total	693	718

experimental module suggests that some of the differences between the insured and uninsured participants may have reflected the change in question format.

It is not our intention to suggest that health insurance status does not have an important effect on health status and disability status. However, because of the change in question format in these surveys, it is difficult to determine the magnitude of the effect from the data used in the analysis. Repeating the analysis with data from 1996 through 2000 would allow the authors to estimate the true effect of insurance on disability with the use of identically worded questions.

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The authors reply:

To the Editor: Harrison and Biddle present data suggesting that changes in the questions about physical functioning in the Health and Retirement Study could have led us to overestimate the rate at which new physical difficulties developed in the participants. They used an "experimental module" from the main 1994 interview as their gold standard to judge the validity of the measured outcomes. This approach is problematic, because although the questions in the experimental module were identical to the questions administered at base line (1992), the mode of administration was different (a face-to-face interview in 1992 in contrast to a self-administered questionnaire in the experimental module in 1994). It is therefore uncertain that the experimental module provides the most valid estimate of the rate of new physical difficulties. Moreover, we measured outcomes with data from the 1996 questions, not the 1994 questions used in the analysis conducted by Harrison and Biddle. It is unclear whether their results can be generalized to the 1996 data, because the 1996 questions had a different set of response options than either the 1992 or the 1994 questions.

It remains possible that changes in the survey questions may have led us to overestimate the true number of persons in whom new difficulties developed, particularly with respect to agility. However, we disagree that the "differences between the insured and uninsured participants may have reflected the change in question format." This would be true only if any misclassification of the outcomes was larger among the uninsured participants than among the insured participants (i.e., if there was differential misclassification bias),[1] and Harrison and Biddle do not present evidence suggesting such a bias. In general, unbiased error in the measurement of an outcome leads to underestimation of the true difference between groups (i.e., a bias toward the null).[1] For example, we reported that the rate of new mobility difficulties was 17.1 percent among the continuously insured participants and 28.8 percent among those who were continuously uninsured. If both of these figures were overestimated by 4 percentage points, then the true rates of new difficulties with mobility would be 13.1 percent and 24.8 percent, respectively. Thus, the correct estimate of the crude relative risk of new mobility difficulties among the continuously uninsured participants as compared with those who were continuously insured would be 1.89, which is substantially higher than our original estimate of 1.68.

Therefore, our findings may have underestimated the increased risk of a decline in physical functioning in uninsured persons. We agree that it is important to examine whether the uninsured participants were at increased risk for the development of new physical difficulty between 1996 and 2000, a period when the questions about physical functioning in the Health and Retirement Study remained the same.

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Research in Developing Countries

To the Editor: Shapiro and Meslin[1] and Koski and Nightingale[2] (July 12 issue) discuss the ethical problems that occur when developed countries sponsor clinical trials in de-

TABLE 1. OVERSEAS-DEVELOPMENT AID IN 1999.*

COUNTRY	AID	
	% of GDP	$U.S. (billions)
Denmark	1.01	1.73
Norway	0.91	1.37
The Netherlands	0.79	3.13
Sweden	0.70	1.63
Luxembourg	0.66	0.12
France	0.39	5.64
Switzerland	0.35	0.97
Japan	0.35	15.32
Finland	0.33	0.42
Ireland	0.31	0.25
Belgium	0.30	0.76
Canada	0.28	1.70
New Zealand	0.26	0.13
Germany	0.26	5.52
Austria	0.26	0.53
Portugal	0.26	0.28
Australia	0.26	0.98
United Kingdom	0.23	3.40
Spain	0.23	1.36
Greece	0.15	0.19
Italy	0.15	1.81
United States	0.10	9.15

*The United Nations has set a target of 0.70 percent of the gross domestic product (GDP).

veloping countries. Many of the ethical problems arise because developing countries are poor and cannot afford the treatments that are used in developed countries. An important ethical issue is therefore the amount of economic aid given by rich countries to poor countries.

The total amount of aid given to developing countries has decreased substantially over the past 10 years. The United States, in particular, now gives a much lower proportion of the gross domestic product (GDP) than any other country that belongs to the Organization for Economic Cooperation and Development (OECD) (and my country, Australia, also gives less than the average amount). Table 1 shows the amount of aid given by each OECD country, with the least generous nations at the bottom of the table.[3] The target for overseas-development aid that has been established by the United Nations is 0.7 percent of the GDP; only Denmark, Norway, the Netherlands, and Sweden meet or exceed this amount.

Perhaps doctors in developed countries could do more to persuade their governments to help developing countries. This would reduce the large disparity in wealth that is the root cause of the ethical problems that arise when clinical trials sponsored by developed countries are conducted in developing countries.

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To the Editor: As chairman of the investigational review board at my institution, I believe the use of a placebo by a U.S. organization administering a clinical trial in a developing country, when the same study performed here would demand a therapeutic control, should be viewed with skepticism. Use of placebo on the grounds that one cannot determine the best alternative to the treatment under investigation or, worse, on the grounds that such use is consistent with the local standard of care — no therapy — is potentially inhumane, even if people are no worse off at the end of the study than they would have been if they had not participated in it.

Conducting a placebo-controlled trial when there is a reasonable therapeutic alternative to the treatment under investigation is most likely to be motivated by financial considerations. In the United States, we have categorically rejected the notion of children working in sweatshops to make clothing. How can we accept the possibility of using drugs that have been tested in trials in underdeveloped countries in which patients in control groups may have suffered or died because they received placebo instead of active treatment?

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Nongenetic Male Pseudohermaphroditism

To the Editor: Mendonca et al. (Oct. 11 issue)[1] conclude that the finding of discordance in growth and genital development in monozygotic twins "convincingly" rules out a genetic cause of male pseudohermaphroditism. There are known genetic mechanisms that could account for the discordance. Fourteen cases of discordance in monozygotic twins have been reported in Beckwith–Wiedemann syndrome.[2,3] Alternatively, a nondisjunction or reduplication event at the time of the first cell division could result in uniparental disomy of a chromosome (i.e., both chromosomes are inherited from either the father or the mother). Maternal uniparental disomy of chromosome 7 has been associated with the Silver–Russell syndrome, which results in decreased weight gain and linear growth, whereas the paternal form has no discernible phenotype. Hypospadias has been reported in Silver–Russell syndrome.[4] One chromosome 7 marker was tested, but it did not provide information that would rule out whole-chromosome uniparental disomy, nor would testing a single chromosome 7 marker rule out segmental disomy due to a somatic recombination involving chromosome 7 homologues before the first cell division, an event that could also result in the same phenotype. Maternal uniparental disomy of chromosome 14 is also associated with growth retardation and genital anomalies.[5] All of these are disorders of imprinting and gene expression (sometimes referred to as epigenetic effects). The limited panel of markers tested to confirm monozygosity in the case described by Mendonca et al. does not rule out uniparental disomy.

The occurrence of a somatic mutation in the affected male twin after the first cell division would be a second potential explanation. This event would result in discordance for a genetic condition. Although the authors may be correct that there are nongenetic causes of this phenotype, to rule out genetic conditions on the basis of the evaluation they describe is not justified.

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The authors reply:

To the Editor: We thank Dr. Williams for explicitly stating some of the hypotheses to which we referred in our report but which were not formally excluded because we

had no plausible clinical basis to do so. We described monozygotic boys, one of whom had reduced prenatal growth, male pseudohermaphroditism, and no other anomalies; there was no clinical evidence of Beckwith–Wiedemann, Silver–Russell, or other syndromes. So far, this constellation has not been observed in children with uniparental disomy of chromosome 7 or 14 (or of chromosome 2, 9, 11, 16, or 20); conversely, the exclusive combination of prenatal growth retardation and incomplete male differentiation — which is not rare — has hitherto not been ascribed to uniparental disomy. Nevertheless, we have now tested the hypothesis that these anomalies were due to uniparental disomy of chromosome 7 or 14 by assessing five markers along chromosome 7 (D7S507, D7S484, D7S519, D7S630, and D7S661) in addition to the previously studied D7S820 and three markers along chromosome 14 (D14S70, D14S258, and D14S280), using an ABI Prism Linkage Mapping Set (Applied Biosystems, Foster City, Calif.). The twins had the same genotype for all assessed markers. Uniparental disomy of chromosome 7 or 14 was ruled out by the presence of informative markers at 7p21, 7q21, 7q35, and 14q23.

In conclusion, this additional evidence, as well as recent data,[1] corroborate our hypothesis that male pseudohermaphroditism, when accompanied by early growth retardation, may not have a primarily or strictly genetic origin. However, we agree that available evidence is insufficient — and is unlikely ever to be sufficient — to rule out the involvement of all the known postzygotic or epigenetic mechanisms or those that have yet to be discovered.

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Reactions to the Events of September 11

To the Editor: Schuster et al. (Nov. 15 issue)[1] report an increased incidence of distress after the events of September 11 and advise clinicians to be prepared to assist people with trauma-related symptoms. Using national workload data from the Department of Veterans Affairs, I compared the average number of daily outpatient visits during the 19 working days before and after September 11 in different clinical subgroups and geographic locations (excluding weekends, holidays, and September 11 itself).

Veterans Affairs facilities in New York City had small, nonsignificant ($P>0.05$) increases in the number of daily visits for general medical care (6.1 percent) and mental health care (5.0 percent), and more specifically for post-traumatic stress disorder (4.3 percent) and substance abuse (5.4 percent). Data from previous years show that these increases were smaller than those for the same period in 2000 (which had an 11.7 percent increase in mental health visits and a 21 percent increase in medical visits) but greater than those observed in 1999 (which had an 11.5 percent decrease in mental health visits and a 0 percent change in medical visits). The small increases in the use of services in 2001 thus differ little from those of previous years and probably reflect the fact that patients, clinicians, or both were returning from August vacations. The 5.0 percent increase in the use of mental health services in New York was slightly smaller than the increases in Washington, D.C. (10.9 percent), other large northeastern cities (15.3 percent), Oklahoma City (6.9 percent), and other large U.S. cities (10.1 percent).

Although the events of September 11 were profoundly traumatic for those directly involved and clearly distressing for others, they are not necessarily medically significant. I found no substantial short-term change in the use of services, even among more vulnerable patients with mental illness or post-traumatic stress disorder. Although we should acknowledge our natural emotional reactions to tragic events, we should not overly medicalize them without justification.

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1. Schuster MA, Stein BD, Jaycox LH, et al. A national survey of stress reactions after the September 11, 2001, terrorist attacks. N Engl J Med 2001;345:1507-12.

The authors reply:

To the Editor: We appreciate Dr. Rosenheck's data on the important issue of the use of health services in the 19 days after the September 11 terrorist attacks. We look forward to future research on the use of health services (as well as on the unmet need for treatment) over longer periods and in settings other than the Veterans Affairs system.

Our study found that many people across the United States had stress reactions during the days after the attacks. It is important for clinicians and others to be aware that such reactions are common and may even occur in people who are far from a disaster. Clinicians can reassure people that their stress symptoms are typical and that they will often resolve without any intervention. Such information is incorporated into most post-trauma mental health interventions.[1,2] Clinicians can also inform their patients about effective coping strategies and give additional attention to those with persistent or particularly severe symptoms. Our study found that most people were using coping strategies that are considered healthy,[2,3] such as talking with others, turning to religion, participating in group activities, and volunteering.

Many people's reactions will dissipate over time and without treatment, although ongoing threats, attacks, and unrelated catastrophes may prolong the process for some. We anticipate that a subgroup of people might have a harder time recovering, because they were directly exposed to the

attacks or because of their personal characteristics (e.g., a history of mental health problems).

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Emergence of Macrolide Resistance during Treatment of Pneumococcal Pneumonia

To the Editor: The emergence of antibiotic resistance during treatment for pneumococcal infection is exceedingly rare.[1] To our knowledge, there is no previous report of a genetically characterized, antibiotic-resistant pneumococcal mutant emerging during therapy and serving as the cause of treatment failure.

A previously healthy 28-year-old man presented with a five-day history of cough and dyspnea. He had hypotension, hypothermia, and rales in the right upper lung. His white-cell count was 14,000 per cubic millimeter (28 percent bands). Chest roentgenography showed infiltrates in the right middle and upper lobe. The sputum contained abundant gram-positive diplococci, and culture yielded *Streptococcus pneumoniae;* blood cultures were negative.

Empirical therapy with 500 mg of azithromycin per day

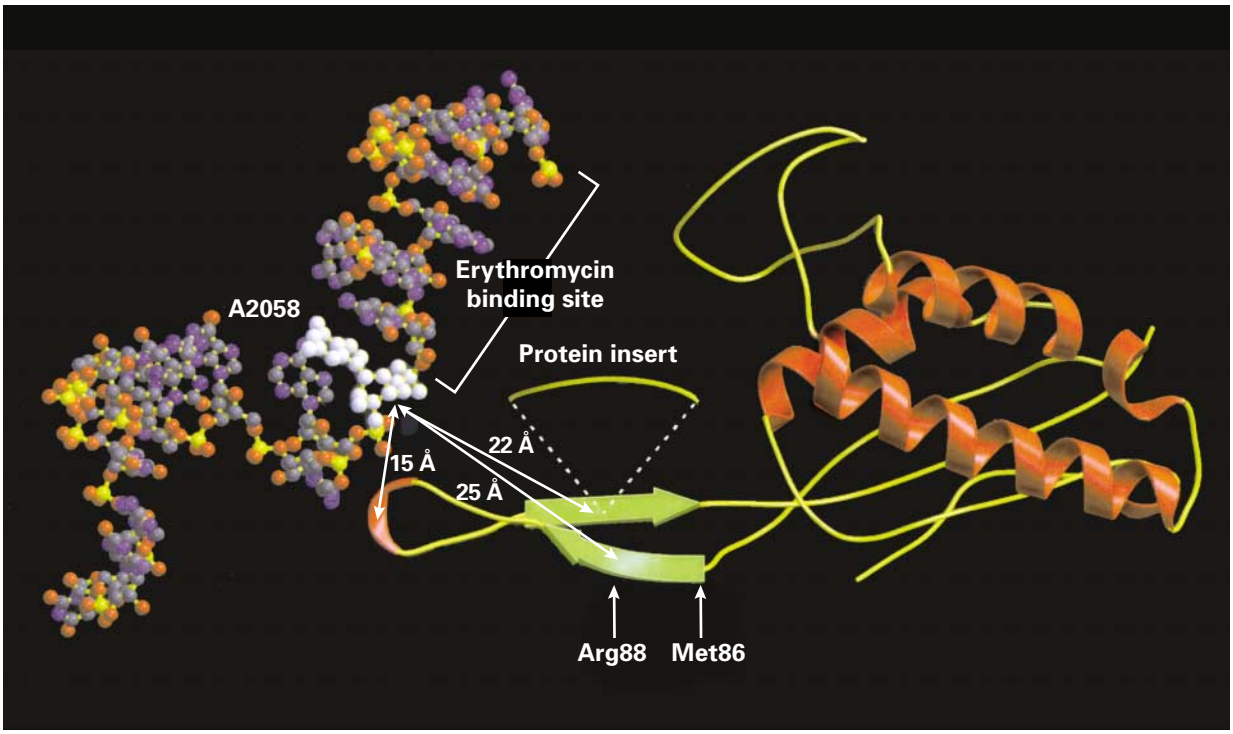

Figure 1. The Macrolide-Binding Site of the Resistant Mutant.

The macrolide-binding site is depicted as a large cavity between the L22 protein (ribbon diagram on the right-hand side) and the 23S ribosomal RNA, near position A2058 (on the left-hand side). The insert of six amino acids encoded by the 18-bp tandem repeat is shown as a green bar. The hairpin region of L22 comes within 15 Å of the 23S base A2058 (identified according to the *Escherichia coli* numbering scheme); the peptide insert is about 22 Å from this region. This insertion is believed to alter the fit of macrolides into the ribosomal pocket. To generate this figure, we aligned the gene for L22 from *Streptococcus pneumoniae* and *Thermus thermophilus,* identifying the location of the six-residue repeat fragment, RTAHIT, after residue 102 in the resistant isolate. We then mapped the location of this insert onto the published structure of L22 from *T. thermophilus*[3] and performed a least-squares superposition of L22 from *T. thermophilus* onto the structure of L22 from *Haloarcula marismortui*[4] in the context of the 23S RNA molecule.

intravenously was begun at admission, and the patient's condition improved rapidly. On the fourth day of treatment, his condition suddenly deteriorated, and hypotension and hypothermia again appeared. Roentgenography revealed extensive right-sided infiltrates and pleural effusion. Cultures of bronchoalveolar-lavage and pleural fluids yielded pneumococcus; blood cultures were negative. Ceftriaxone and vancomycin were administered, but multiorgan failure developed, and the patient died. His relatives declined to give permission for an autopsy.

The isolates of *S. pneumoniae* from the initial sputum sample and from pleural fluid obtained at the time of relapse were serotype 3 and were identical on BOX polymerase chain reaction (BOX elements are interspersed repetitive DNA sequences in *S. pneumoniae*) and ribotype analysis.[2] The initial isolate was fully susceptible to all antibiotics tested, including penicillin (minimal inhibitory concentration [MIC], <0.016 μg per milliliter), clindamycin (MIC, 0.008 μg per milliliter), erythromycin (MIC, 0.015 μg per milliliter), azithromycin (MIC, 0.008 μg per milliliter), and quinupristin–dalfopristin (MIC, 0.12 μg per milliliter). In contrast, the later isolate, although still susceptible to penicillin and clindamycin, was resistant to erythromycin, azithromycin, and quinupristin–dalfopristin (MIC, 2 to 4 μg per milliliter). Neither isolate contained *erm*(B) or *mef*(A),[3] two determinants of erythromycin resistance.

Genes encoding 23s ribosomal RNA and ribosomal proteins involved in macrolide binding were sequenced. The gene for ribosomal protein L22 in the macrolide-resistant mutant contained an 18-bp tandem repeat that was not present in the original isolate. This insertion resulted in the duplication of six amino acids — $_{102}$KRTAHITRTAHITVA$_{116}$ — adjacent to the macrolide-binding site on the 23s RNA (Fig. 1). No other mutations were identified.

Macrolides inhibit bacterial-protein translation by inserting themselves into a pocket of the 23S ribosomal subunit at the site of protein assembly. Most macrolide-resistant pneumococci alter the macrolide-binding site by *erm*(B)-encoded methylation of A2058 or exclude macrolides by a *mef*(A)-encoded efflux pump.[5] Mutations that alter protein sequences in this pocket may, however, cause macrolide resistance, as has been demonstrated for ribosomal proteins L4 and L22.[6,7] We hypothesize that, in the mutant strain from this patient, the six-amino-acid repeat in L22 disrupts the binding cavity by altering the tertiary structure of the hairpin (Fig. 1). The mutation occurred during therapy, causing a relapse that was fatal.

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