incorrectly stage their patients. I think any surgeon who attempts this procedure should only do it as part of a trial with an axillary lymph node dissection so that he/she can assess his/her own success and not miss lymph node metastases. Our Fellows are being trained adequately in this technique and should be effective in promoting its accuracy. In addition, we are planning a multicenter trial during which investigators will be taught the technique. I am not sure a didactic course is the best venue to teach this procedure, but we are considering that as well.

I appreciate Dr. Noguchi's comments and his insightful observations.

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June 7, 1995

Dear Editor:

We read with interest the article by Busch et al.[1] The authors are to be commended for conducting a very well-designed clinical trial. According to some reports in the literature, most of which are retrospective, allogeneic blood transfusions are associated with a poor prognosis for patients who are undergoing operations for colorectal cancer.[2–5] Busch et al.[1] conducted their trial in an attempt to determine whether autologous blood transfusions would reduce the rate of recurrence of colorectal cancer and improve survival as compared with allogeneic transfusions. They published at least three articles reporting on this hypothesis.[1,6–7]

The first article is entitled "Blood Transfusions and Prognosis in Colorectal Cancer," and was published in the May 1993 issue of the *New England Journal of Medicine*.[6] This article contains a detailed presentation of the methodology used and focuses on the survival outcome. The authors found no difference between autologous and allogeneic transfusion groups in 4-year survival rates. However, this failure to find any statistically significant difference could be a function of insufficient sample size. The authors' detailed presentation of the methodology contained no sample size estimate. Clinical trials require a large number of subjects. The finding of no difference in survival rates between the two transfusion groups must be supported by a sample size estimate to show that they had sufficient power to detect a statistically significant relationship should one have been present.

In the second article,[1] after reiterating the findings from the first article, the authors combined the two transfusion groups and looked for an association between having had one or more transfusions (regardless of type) and either local or distant metastases. The results section focuses mainly on the univariate analyses. When the two transfusion groups were combined, the authors lost their randomization scheme. When this happens, one can no longer expect the groups to be comparable on all potentially confounding variables. One must control for potentially confounding variables, usually by stratification or multivariate modelling in the data analysis. The authors used multivariate modelling, but they tested the wrong models. The four univariate predictors of local tumor recurrence rate are: type of operation, Duke's stage, blood loss, and blood transfusion. From Table 4, it *appears* that these four separate independent predictors were tested two at a time in three separate models in an attempt to predict local recurrence rate. It would be much more appropriate to test all four independent predictors simultaneously using one four-factor model.

Also, the title of this article is misleading. The criteria for a noncausal or indirect relationship include: 1) a statistically significant association between two variables and 2) the presence of a known or unknown third variable, common to both of the other two variables, which actually is the cause of the association between the first two variables.[8] The statistically significant association between two variables, as stated in the title, is between blood transfusions and local tumor recurrence. The possible third or confounding variable, as presented in the discussion section, may be failure of the surgical technique which accounts for the necessity of the blood transfusion and may be the real cause of the local tumor recurrence.[9] But as we discover in a footnote to Table 4,[1] once blood loss is taken into account, the association between blood transfusion and local recurrence rate disappears. The first criterion for a noncausal or indirect relationship, then, is violated. The second criterion, however, may still apply.

McArdle and Hole[9] demonstrated that local recurrences are largely a failure of surgical technique that results in tumor spill. It is well known that violation of tumor planes, whether in the mesentery or by inadvertent lumenal entry, can result in markedly increased local recurrence rates and decreased survival rates. These local factors may be difficult to identify, however, particularly retrospectively. Several other studies[10–12] have suggested more strongly that blood transfusions are associated with recurrence of cancer. But these also have failed to examine local factors that may very well be the true determinants of increased recurrence rates. Prospective data collection on such local factors should be the focus of future studies.

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April 20, 1996

Dear Editor:

We thank Dolezal et el. for their reaction to our article on the noncausal relationship between blood transfusions and local recurrence in colorectal cancer.[1] Their doubts about the sample size of our study is incorrect. We performed power calculations before the start of our study, which indicated that 500 patients were required (actually 510 patients were enrolled). We agree that no trial should be started without a prior evaluation of the probability that the study would detect a statistically significant difference of interest. Because various assumptions have to be made, these calculations are rather speculative. However, immediately after the trial is finished, these power calculations become obsolete. Whether the completed trial was big enough can be read from the confidence limits. We have shown[2] that the 95% confidence interval for the difference (autologous group − allogeneic group) of the 4-year colorectal cancer survival percentages ranges from +7% to −18%. Although some advantage in using autologous blood cannot be precluded from our data, it appears that our sample size was large enough to demonstrate that such advantage would be very minor at most.

We do not agree with Dolezal et al. that the most appropriate Cox regression model would be the one that includes both the factor blood transfusion and blood loss. Obviously, both factors are strongly correlated. The percentage of patients who received blood transfusions in the group with blood loss <500 mL, 500 mL to 1000 mL, and >1000 mL were 31%, 72%, and 96%, respectively (these three groups were approximately the same size). When such strong relationship is present (this is called multicolinearity in the statistical literature), it is extremely difficult to separate the effects of both factors.[3] Table 1 shows the results of the multivariate analysis of the four factors indicated.

Allowing for blood loss, the effect of the variable blood transfusions is not significant. However, significance is achieved when blood loss is not taken into account. When both these factors are tested in a four-factor model, their joint significance is p = 0.046. However, their separate contributions cannot be assessed reliably because of their strong correlation. Because both factors are roughly presenting "the same thing," we decided to present the outcomes of the model without blood loss in detail, and supplied a footnote describing the four-factor model, which seems appropriate. Nevertheless, whether or not factors are related causally to the local recurrence rate cannot be demonstrated from these analyses, irrespective of the outcomes. There always may be some hidden factors that are the real determinants. The probability of these factors is discussed in our article. Only the risk of local recurrence was related significantly to blood transfusions, whereas no such relation could be demonstrated for distant metastases. On bases of the immunologic hypothesis, it is very unlikely that blood transfusions only would influence the local situation. The explanation that local factors affect the need for blood transfusions and the risk of local tumor recurrence is more logical.

Table 1. COX REGRESSION OF LOCAL RECURRENCE RATES ALLOWING FOR FOUR FACTORS*

Factor	Relative Local Recurrence Rate			p Value		
Blood transfusions						
No	1			—		
Yes	3.8	(5.2)		0.06	(0.008)	
Dukes' stage						
A	1			—		
B	2.1	(2.2)	[2.2]	0.20	(0.16)	[0.17]
C	4.6	(5.1)	[4.5]	0.007	(0.004)	[0.007]
Operation						
Intra-abdominal	1			—		
Rectal involvement	1.6	(2.0)	[1.7]	0.31	(0.10)	[0.25]
Blood loss						
<500 mL	1					
500–1000 mL	1.3		[2.4]	0.68		[0.15]
>1000 mL	1.9		[4.2]	0.35		[0.02]

* Outcomes not considering blood loss are given in parentheses, and outcomes not considering blood transfusions are given in brackets.

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