content, usually isotonic. Confining overload to the circulatory or “blood” volume requires overtreatment with whole blood, plasma, and other iso-oncotic products. Although “congestion” on this basis alone was once spoken of, it is a now a rare event.

Until the pulmonary edema edema associated with the transfusion of packed RBCs and plasma derivatives (TRALI) is reported to occur with accurate infused volumes of crystalloid and colloid, and concurrent changes in patients’ weights, it is not going to be possible to distinguish ARDS from acute lung injury and TRALI.

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REFERENCES
2 Barnard RD. Indiscriminate transfusion: a critique of case reports illustrating hypersensitivity reactions. N Y State Med J; October 15, 1951; 2399

Low-Molecular-Weight Heparin and Outcomes

To the Editor:

Conceptually, the suggestion by Alifano et al1 (August 2004) is especially compelling from both the scientific and clinical observational standpoints. However, one needs to carefully consider if low-molecular-weight heparins (LMWHs) are the best choice of drugs to conduct such an important study. First, not all LMWHs are the same, and hence should not be lumped together as one group. Second, and more importantly, there is strong scientific evidence that the biological activities of heparins, beyond anticoagulation, including activities such as antiplatelet, antiangiogenic, and antiinflammatory, are related to the molecular weight of heparin or more precisely to the high sulfate to carboxylate ratio of heparin (unfractionated heparin [UFH]) is more heavily sulfated than LMWHs and has thus the highest ratio. This has been observed in relation to the cellular release of tissue factor pathway inhibitor, the down-regulation of vascular endothelial growth factor and endothelial growth factor, and the inhibition of the c-fos gene, reverse transcriptase, telomerase, and topoisomerase, as examples.3–6 The clear advantages of LMWHs relate to their predictable pharmacokinetics and the convenience of being able to administer the drug subcutaneously in an outpatient setting without the need for routine monitoring. In terms of efficacy and safety LMWHs and UFH are equivalent. While LMWH will provide for equivalent anticoagulation to UFH, we may lose an opportunity to grasp the real usefulness of the parent drug (UFH) from which the LMWHs have been sliced.

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REFERENCES
5 Engberg H. Actions of heparin that may affect the malignant process. Cancer 1999; 85:257–272

To the Editor:

We thank Dr. Arbit for his thorough comments on our article, which basically support the idea on the possible importance of a prospective study on heparin treatment in patients undergoing lung resection for non-small cell lung cancer (NSCLC). In Dr. Arbit’s opinion, unfractionated heparin (UFH) should be probably preferred to low-molecular-weight heparins (LMWHs) because of better in vitro antineoplastic and antiangiogenic properties. We took carefully into account the possibility of such a criticism to our proposal, and we even hypothesized in the published article that the “nonspecific protein binding” of UFH might be necessary for its putative anticancer activity. However, we commented on the efficacy of LMWHs in inhibiting selectins, although to a lesser extent than UFH. We hypothesized that this disadvantage should be compensated by the better bioavailability and more consistent serum levels of LMWHs.

It has been reported that tinzaparin, a LMWH, is particularly effective at releasing tissue factor pathway inhibitor, thus providing further experimental evidence on the potential role of this LMWH as an antitumorigenic agent.1 Even more recently, Mousa and Mohamed2 confirmed this data and demonstrated that tinzaparin is a potent inhibitor of angiogenesis.

In our article, we also pointed out that a few randomized studies evaluated the impact of LMWHs on survival of cancer patients. We quoted the study by Von Tempelhoff et al.,3 who provided evidence that cetroparin, a LMWH, more favorably affected the survival of operated patients with pelvic or breast cancer as compared to UFH. Since the submission of our article, two studies have been published on the impact of dalteparin, another LMWH, on survival of cancer patients. A randomized clinical trial4 of combination chemotherapy with and without dalteparin in small-cell lung cancer showed that the association resulted in significantly improved progression-free survival and overall survival. In the Fragnin Advanced Malignancy Outcome Study,5 which included patients with different kinds of malignancy and adopted no restriction on concomitant use of chemotherapy or radiotherapy, a trend toward improvement in survival (not reaching significance) was observed in patients receiving dalteparin as compared to patients receiving placebo. In this study, analysis of a group of patients with a better prognosis and who survived > 17 months showed that dalteparin treatment was associated with a significant survival advantage.

These last studies should further prompt us to undertake a trial in patients with resectable NSCLC, the subset of NSCLC patients with better prognosis. Which LMWH should be preferred for such a trial is difficult to say. The few available clinical studies...
studies might support the use of certoparin or dalteparin, although experimental data tend to suggest that most LMWHs share anticancer activity.

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References

Testing Lung Function Decline to Time Lung Transplantation

To the Editor:

Timing of referral for lung transplantation for patients with end-stage lung disease from cystic fibrosis (CF) remains a difficult issue. The recent publication by Rosenbluth et al1 proposes a method for timing referral of patients for wait listing. Using at least 4 years of previously measured percentage of predicted FEV1% (FEV1%), Rosenbluth et al suggest using a linear regression model to predict when FEV1% drops to <30% of predicted and suggest listing patients for transplantation 2.11 years prior to that point in order to minimize deaths due to late referrals for lung transplantation.

We have two serious concerns regarding this work. First, the linear regression model proposed is not validated and may lack predictive power. Second, even were this model predictive, elimination of late referrals for lung transplantation will not change the inability of the FEV1% criterion by itself to identify patients who will have survival benefit from transplantation.

To examine these issues, we undertook validation of the proposed model and projected the outcomes for patients likely to receive referral for transplantation using the Rosenbluth model. We used the CF Foundation Patient Registry (CFPR) to identify the 5,408 patients in 1999 who had at least 4 prior consecutive years of FEV1% data, did not undergo transplantation prior to December 31, 2001, and had FEV1% data in 2001. We used linear regression (based on the highest measured FEV1% in a given calendar year) to predict the FEV1% in 2001. Using additional data from the CFPR, we calculated the 5-year predicted survival2 of each patient for 2001 to see how well the proposed model chooses patients for lung transplantation. Figure 1 compares predicted change in FEV1% with actual change in FEV1% between 1999 and 2001. Among the patients shown in Figure 1, there were 458 patients that were predicted to have an FEV1% <30% in 2001. Figure 2 shows the actual FEV1% values in 2001 for those 458 patients compared to their 5-year predicted survivals in 2001.

These results allow us to address our two concerns. First, the method should be accurate in predicting that FEV1% will be <30% in 2001. Unfortunately, there was no correlation between predicted and actual changes in FEV1% (Fig 1). For patients predicted to have an FEV1% <30%, 45% of the actual FEV1% values in 2001 were >30% (Fig 2). As we have shown previously, this is due to the low predictive power of linear regression to predict future FEV1%.

Second, of all patients identified by Rosenbluth et al1 as good candidates for lung transplantation using FEV1% <30%, only 15% would have predicted improved survival, while 22% would have predicted unchanged survival, and 63% would have predicted reduced survival based on their 5-year predicted survivals (Fig 2). In fact, even if we restrict attention to those 55% of patients who actually have FEV1% <30% in 2001, fully half of those patients selected are not appropriate candidates for transplantation. We base these conclusions on our previous finding that using FEV1% by itself cannot identify a group of patients that has survival benefits from transplantation.4 In contrast, our 5-year predicted survival model does identify a group that triples its survival due to transplantation (Liou et al,4 Figure panels A and F).

Rosenbluth et al1 have cited our work4 as justification for using FEV1% <30% as a criterion for lung transplantation because those who had benefit from the procedure also had a mean FEV1% <30%. Although the group that we chose for transplantation in our work had an FEV1% of 23% (calculated from Table

FIGURE 1. The actual changes in FEV1% between 1999 and 2001 for 5,408 patients are compared to the predicted changes in FEV1%. Predictions were derived by linear regression from FEV1% values from 1996 through 1999. The dashed line shows the expected relationship between predicted and actual changes.

FIGURE 2. The actual FEV1% values in 2001 for those 458 patients compared to their 5-year predicted survivals in 2001.