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In Reply:—We agree with Block and Ghoneim that this phenomenon needs further investigation and that the dose-dependent effects of the commonly used anesthetics on implicit memory should be determined by future studies.

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Is Aprotinin Worth the Risk in Total Hip Replacement?

To the Editor:—We read with interest and some misgivings the report by Janssens *et al.*[1] on 40 patients undergoing total hip-replacement surgery who, in a randomized and double-blind study, intravenously received either aprotinin (2×10^6 KIU followed by an infusion of 5×10^5 KIU/h, n = 20) or placebo (normal saline, n = 20). Patients receiving aprotinin had a 26% decrease in perioperative blood loss and a 47% reduction in perioperative transfusion requirements compared to the placebo group ($P < 0.05$ and $P < 0.001$, respectively). The study suggests an expansion of the indications for aprotinin that is neither supported by the results presented nor can be accepted without reservations. We would like to make the following comments.

1. The perioperative blood loss associated with total hip arthroplasty is, among other factors, dependent on the experience of the surgeon, the surgical technique used (approach, osteotomy of the greater trochanter, the degree of surgical hemostasis), and the type of prosthesis used (cemented or cement-free prosthesis). Janssens *et al.* reported that all procedures were carried out by the same surgeon but did not state whether the groups were comparable with regard to the technical surgical factors mentioned above. Without this information, postulation of a causal relationship between the significant difference in perioperative total blood loss and the use of aprotinin must be regarded as pure speculation. A significant difference in perioperative total blood loss also has been found by other authors, including Wittig *et al.*[2] in a randomized study of 40 patients undergoing total hip arthroplasty (median 1,430 ml *vs.* 2,175 ml, representing a reduction of 34%; $P < 0.05$). Their patients differed only with regard to the modalities of preoperative autologous blood donation, and no patient had received aprotinin.
2. The lower perioperative total blood loss in Janssens *et al.'s* aprotinin group was due to a significantly lower *intraoperative* blood loss. In a study of similar design, Wollinsky *et al.*[3] found that the *postoperative* blood loss was significantly lower in the aprotinin than in the control group (difference in mean ca. 300 ml, $P < 0.01$). They suggested that aprotinin should be able to primarily reduce the *postoperative* blood loss, which would be more in keeping with the experience with aprotinin in cardiac surgical patients. The *postoperative* external blood loss, however, was not significantly different between the aprotinin and placebo groups in the study by Janssens *et al.* This finding also leads us to doubt whether the observed difference in the blood loss may be attributable to a specific pharmacologic action of aprotinin.
3. Janssens *et al.* reported a considerable perioperative blood loss in both the aprotinin and placebo groups (1,446 ± 514 ml and 1,943 ± 700 ml, respectively). A similar blood loss was observed in the study of Wollinsky *et al.* (mean 1,578 and 1,952 ml, respectively). In a series of 49 consecutive patients undergoing *cement-free* total hip arthroplasty *without aprotinin,* we found a perioperative total blood loss of 1,245 ± 412 ml, which was 14% less than in the aprotinin group of Janssens *et al.* This may be due to a much shorter surgical time (100 ± 33 min in our series *vs.* 169 ± 27 min in the study by Janssens *et al.*) and to the surgical technique used. We wonder whether the postulated reduction in bleeding after aprotinin could be demonstrated when perioperative blood losses *per se* are smaller.
4. Janssens *et al.* conclude from their study that the combination of high-dose intraoperative aprotinin and the preoperative donation of 3 units of autologous blood would allow 90% of patients undergoing total hip arthroplasty to avoid homologous blood transfusion. The perioperative transfusion requirements in the aprotinin group were 1.8 ± 1.2 units of blood per patient, which may be considered a typical amount for this procedure,[4] even without aprotinin. As already demonstrated by several authors,[2,5] these requirements may be covered solely by the preoperative donation of 3 units of autologous blood, thus avoiding any homologous blood transfusion in 90% of the patients without recourse to using aprotinin. When additional intraoperative blood salvage is used, up to 95% of patients may undergo surgery without receiving

homologous blood transfusions.[6] In our opinion, it is better policy to initially employ, along with blood-sparing surgical techniques, the full spectrum of conventional methods of blood conservation (preoperative autologous blood donation, isovolemic hemodilution, perioperative blood salvage) in an attempt to avoid homologous blood transfusion.

5. A particularly undesirable effect of aprotinin is immunologic sensitization. The patient receiving aprotinin today for a total hip arthroplasty may be your patient tomorrow! For example, a cardiac surgical patient in our department suffered a fatal analphylactic shock after infusion of aprotinin. Unknown to this patient, she had received aprotinin during a tonsillectomy some months earlier. The risk of anaphylactoid reactions after previous exposure to aprotinin, though not necessarily fatal, is quoted as 0.5% by the manufacturer. In the literature, figures range between 1% and 9.1%[7] for such a reaction. By contrast, the incidence of hepatitis C after blood transfusion is less than 1:3.000, the risk of HIV infection is quoted as 1:225,000 to 1:1 million, and the total mortality of transfusion-transmitted infections is given as 1: 260,000.[8,9] Thus, on a critical risk-benefit basis, we seriously doubt the justification of aprotinin administration in total hip arthroplasty. We would challenge the postulated reduction in perioperative blood loss as a reasonable indication for aprotinin, as long as

- valid numbers are missing, which would prove the necessity for aprotinin with respect to its overall risk
- inexpensive, simple, and reliable screening tests for aprotinin sensitization are not available
- there is no reliable prophylaxis against severe anaphylactoid reactions after aprotinin exposure

The proposed red mark "aprotinin used" in the discharge letter of patients having been exposed to aprotinin[10] would appear to be of only limited value. Avoid having to use such warning in the first place!

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In Reply:—We agree that perioperative blood loss associated with total hip arthroplasty depends on the surgical technique and the experience of the surgeon. In our study, Moore's posterolateral approach with osteotomy of the greater trochanter was used in all patients. The prosthetic materials were either cemented or noncemented with cancellous screws used to secure the acetabular component. Cemented prostheses were distributed equally between the two groups [7 in the aprotinin (A) group, 10 in the placebo (P) group]. No significant difference in total bleeding was noted between the cemented and noncemented prostheses in both groups. However, in group P, early postoperative blood loss (during the first 5 h postoperatively) was significantly greater in the case of cement-free prosthesis as compared with cemented prosthesis (525 ± 247 ml *vs.* 330 ± 119 ml, $P < 0.05$). In group A, blood loss associated with noncemented prostheses was significantly greater as compared to cemented prostheses during the postoperative period between 5 and 24 h (322 ± 161 ml *vs.* 147 ± 94 ml, $P < 0.05$). A multiple regression statistical analysis demonstrates that, intraoperatively, only treatment