1. If the conclusion was that aprotinin could reduce formation of thrombin (as measured by thrombin–antithrombin III complexes (TAT)), then more detailed results of the TAT assays in the study groups should be provided in order to support these conclusions.
2. The authors propose a significant reduction in thrombin formation as a result of inhibition of the intrinsic system of coagulation. This should have resulted in the preservation of fibrinogen levels in the aprotinin-treated group. Unfortunately, fibrinogen levels were either not measured or not reported.
3. The authors conclude that the levels of fibrinogen–fibrin split products and the split products of cross-linked fibrin (D-dimers) were significantly reduced because of attenuated proteolytic activities of *thrombin and plasmin* in the treated group. We propose that the decreases in the treated group could have resulted solely from aprotinin's inhibition of plasmin. One should consider that during cardiopulmonary bypass, fibrin is still deposited on artificial surfaces but is subjected to decreased fibrinolysis during aprotinin treatment. Thus, the reduced levels of fibrin degradation products in the treated group may have resulted from decreased fibrinolytic activity, rather than from decrease in the activity of *both* thrombin and plasmin.
4. If the authors assume that inhibition of kallikrein activity can be achieved only by "high-dose" aprotinin during cardiopulmonary bypass (CPB), then they assume that other endogenous inhibitors of the kallikrein system (*e.g.*, α-2-macroglobulin) are rapidly consumed or rendered ineffective during CPB. It is necessary to document preservation of plasma prekallikrein levels with aprotinin therapy during CPB to better support this hypothesis.

Although several investigators have demonstrated a reduction of postoperative blood loss in patients undergoing cardiac surgery and treated with aprotinin,[2,3] we believe that the exact mechanism of aprotinin's effect is still not well understood, as demonstrated by the above issues. If the conclusions of Dietrich *et al.* (*i.e.*, the reduction by aprotinin of thrombin formation) are true, one might assume that inhibition of the intrinsic pathway of coagulation by aprotinin during CPB could predispose patients to hemorrhage in the intraoperative period. Paradoxically, the findings in this particular study showed that intraoperative blood loss during aprotinin treatment was decreased (636 ± 322 ml [control] *vs.* 363 ± 159 ml [aprotinin treated]).

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In Reply:—Allison and Whitten raise some important questions concerning coagulation patterns during high-dose aprotinin treatment.

1. The course of the thrombin–antithrombin III complexes (TAT) during cardiopulmonary bypass (CPB) clearly demonstrated less thrombin formation during CPB under aprotinin treatment. We provided the TAT concentrations of all patients (fig. 3).[1] There was a significant correlation between the TAT concentration at the end of CPB and the intraoperative blood loss in the control group, whereas this correlation was not significant with aprotinin. Fibrinopeptid A, which is a very sensitive thrombin marker, was significantly increased at the end of CPB in the control group in comparison to the aprotinin group (22.0 ± 22 ng/ml in the aprotinin group *vs.* 11 ± 7 ng/ml in the control group; $P < 0.05$). Similar results were found by others.[2] Because of problems in the preanalytic phase we regard the TAT results to be more conclusive than the FPA concentrations. Therefore, only the TAT concentrations were provided.
2. Fibrinogen levels were measured but not reported since there were no significant differences between the groups. However, due to the acute phase reaction, fibrinogen is a very insensitive marker for the activity of thrombin and plasmin. After completing the study we determined the concentration of plasma fibrin by means of a fibrin-specific monoclonal antibody: at the end of CPB it was 15.0 ± 17 ng/ml in the control group, compared to 3.2 ± 2 in the aprotinin group ($P < 0.05$). These results are conclusive for the prevention of fibrin formation by aprotinin.
3. We measured prekallikrein levels and could not demonstrate significant differences at the end of CPB (42 ± 11 *vs.* 39 ± 6%, control *vs.* aprotinin). However, this is not surprising, because aprotinin does not inhibit the conversion from prekallikrein to kallikrein; it acts on the level of kallikrein and inhibits the action of kallikrein. Therefore, we could measure a significant difference in the concentrations of the α_2-macroglobulin complexes with kallikrein (2.3 ± 2.1 ng/ml vs. 1.3 ± 3.9 ng/ml at the end of extracorporeal circulation and 3.7 ± 2.7 *vs.* 0.9 ± 3.1 ng/ml at the end of operation, control group *vs.* aprotinin; $P < 0.05$).
4. These results taken together seem to justify the conclusion that the reduction of split products of the crosslinked fibrin (D-dimers) was due to attenuated proteolytic activity of thrombin and plasmin. It must be emphasized that activation of the intrinsic pathway of coagulation results not only in activation of coagulation but also in

activation of fibrinolysis. Therefore, the antifibrinolytic activity of aprotinin is due not only to its antiplasmin properties but also to the inhibition of kallikrein.

5. We believe that our results provide strong evidence that inhibition of the contact activation of coagulation is the main aspect of aprotinin's effect on blood loss. This is supported by the prolongation of the global coagulation tests of activated clotting time and activated partial thromboplastin time. The reduced intraoperative blood loss with aprotinin does not contradict this, because it is well known that the inhibition of the intrinsic pathway of coagulation does not lead to an increased bleeding tendency. The reduction in bleeding tendency with aprotinin is caused by better-preserved coagulation patterns, which lead to less stimulation of platelets and therefore better preserved platelet function.

It was beyond the scope of our article to provide all data that led to our conclusions. We agree with Allison and Whitten that more studies are needed to delineate the precise mode of action of aprotinin. We hope, however, that our study has contributed to this end.

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Effects of Aprotinin on Postoperative Bleeding

To the Editor:—In a recent study,[1] Dietrich *et al.* studied the effects of high-dose aprotinin treatment in 20 patients undergoing cardiac surgery. They found an important decrease of postoperative bleeding and consumption of blood products during the peroperative and postoperative periods when compared to a control group.

We have performed a comparable study in two groups of 25 patients (aprotinin and control) with the same protocol. Our results concerning total postoperative bleeding and homologous blood requirement are identical to those of Dietrich *et al.*, as are results concerning clotting parameters. We agree with the authors about the interpretation of the important decrease of the complex of thrombin with antithrombin III (TAT) and of D-dimers in the aprotinin group. However, we think that the important reduction of D-dimers we have observed in our study also may be explained by a direct inhibiting effect of aprotinin on the produced plasmin.

In addition, we measured the fibrinolytic activity in the preoperative period by the euglobulin clot lysis time (ECLT). The responders were defined by a 30-min reduction of ECLT after 20-min venous stasis, compared with the same test before stasis. The results at the end of the first postoperative hour and total bleeding are shown in the table 1.

Although we have not observed any difference on tissue plasminogen activator (tPA) concentration (data not shown), it seems difficult to eliminate a vascular wall involvement in inhibition of fibrinolysis by aprotinin. Indeed, our results suggest an efficacy of aprotinin mainly during the early postoperative period. The small number of patients and the effects of other treatments on bleeding might explain the lack significance on total bleeding. It is well recognized that the response to venous stasis (as a responder or a nonresponder) depends on a balance between tPA and plasminogen activator inhibitor (PAI).[2] Our preliminary results show a better PAI activity in the aprotinin group.

TABLE 1. Bleeding after Aprotinin or Placebo

	Group	Placebo	Aprotinin	
H1	NR	193 ± 80	182 ± 56	
	R	375 ± 294	179 ± 82	$P < 0.05$
T	NR	883 ± 267	872 ± 354	
	R	1382 ± 1000	755 ± 340	NS
	NR + R	1157 ± 593	799 ± 59	$P < 0.05$

Postoperative bleeding (milliliters, means ± SD) from insertion of chest tubes to the end of the first postoperative hour (H1), and total bleeding (T) in responder patients (R), nonresponder patients (NR), and both groups. NS = not significant.

Additional studies are needed to determine wether aprotinin effects are caused by an anti-tPA effect[3] or a decreased urokinase plaminogen activator secondary to an antikallikrein effect of aprotinin.

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