Prothrombin Complex Concentrates: Potentially Thrombogenic Materials and Clues to the Mechanism of Thrombosis In Vivo


Factors affecting the coagulant activity of two different prothrombin complex concentrates have been investigated using a sensitive in vitro assay developed in this laboratory. One concentrate contained substantial amounts of potentially thrombogenic material, while the other, which was deliberately fortified with antithrombin III and heparin during production, was judged to be relatively nonthrombogenic. The coagulant activity of the thrombogenic concentrate has been partially identified and was due largely to the presence of coagulation factors IXa and Xa. Neither concentrate contained detectable thrombin. However, after incubation with calcium or various polyamines, large amounts of additional coagulant material, including thrombin, appeared. Heparin and antithrombin III not only neutralized the thrombogenic materials present in the thrombogenic concentrate, but also inhibited the de novo generation of coagulant enzymes during incubation with calcium. The implications of these studies on the preparation of prothrombin complex concentrates and on host susceptibility to thrombosis during the clinical use of these concentrates is discussed.

CONCENTRATES of vitamin K-dependent clotting factors, so-called prothrombin complex concentrates (PCC), are available for use in patients with acquired or inherited deficiencies of one or more of these factors. Despite the therapeutic efficacy of these fractions, several potentially lethal complications have occurred with their use. Rare cases of anaphylactoid reactions have been reported following administration of PCC.1,2 There is, in addition, a very high incidence of hepatitis.3-12 Recently, attention has focused on thrombotic episodes occurring during use of these preparations: arterial thrombosis,13,14 venous thromboembolism,14,15 and diffuse intravascular coagulation18,23 have all been reported with domestic, as well as foreign concentrates.

The nature of the materials responsible for inducing this hypercoagulable...
state is uncertain. We have previously reported studies demonstrating large amounts of unidentified materials in PCC that markedly shorten the clotting time of non-contact-activated plasma and have shown that the quantity of this material correlates well with a tendency toward thrombosis in vivo. Preliminary studies have indicated that these materials are activated clotting factors. The present study deals further with the identity of the coagulant material present in these concentrates and examines some factors important in the generation of such material.

MATERIALS AND METHODS

PCC were obtained from Hyland Laboratories, Costa Mesa, Calif. (Lots #0581T063A1 and #0581T017A1), and the Blood Research Laboratory of the American Red Cross, Bethesda, Md. (PTC #3). The Hyland product was the same lot that was recently associated with a thrombotic fatality and therefore appeared to possess thrombogenicity in vivo. Both concentrates were reconstituted at concentrations of 10–20 mg/ml, corresponding to approximately one-third to one-half the protein concentration of solutions prepared for therapeutic use. Lyophilized antithrombin III (Lot #2) was obtained from the American Red Cross Production Laboratory, Bethesda, Md., and was reconstituted according to directions. Rabbit antiserum against human antithrombin III was obtained from Behring Diagnostics (Somerville, N.J.).

Fibrinogen was purchased from Sigma Chemical Company, St. Louis, Mo., and was 72%, clottable. Sodium heparin (135 units/mg) was supplied by Grand Island Biological Co., Grand Island, N.Y. Phenylmethylsulfonyl fluoride (PMSF) was obtained from the Pierce Chemical Company and was dissolved in absolute methanol at a concentration of 6.4 mg/ml (0.04 M) prior to use. The final concentration of PMSF in the experiments was 0.004 M. Soybean trypsin inhibitor (SBTI) was obtained from the Worthington Biochemical Corporation and was used at a final concentration of 0.01 mg/ml. 1-chloro-3-tosylamido-7-amino-L-2-heptanone (TLCK) was obtained from the Sigma Chemical Company and was used at a final concentration of 0.001 M at pH 8.0. Poly-L-lysine hydrobromide of molecular weight 22,700 was obtained from Miles Yeda Laboratories, Inc. Diethylamino ethyl (DEAE) ion exchange cellulose was supplied by Schleicher and Schuell, Keene, N.H. All other chemicals were of reagent grade and were utilized without further purification.

Partially purified human factor Xla was prepared and assayed by previously described methods. A polyclonal IgG antibody to factor IX used in this study has been shown to bind with normal factor IX and factor Xa as well as the biologically effete factor IX found in some males with hemophilia B.

Anti-antithrombin III was covalently linked to agarose in the following manner. Approximately 5 ml packed bed volume of omega-amino hexyl agarose was washed exhaustively in 0.1 M NaHCO₃ and then suspended in 10 ml 0.1 M NaHCO₃ at pH 8.31; 3 ml anti-antithrombin III antiserum was added to the agarose with constant stirring. At 1-hr intervals, 5 mg ethyl dimethylamino propyl carbodiimide hydrochloride (Pierce Chemical, Rockford, Ill., Lot #4182-10) was added to the antiserum-agarose mixture. The pH was maintained at 8.31 during the coupling procedure. After approximately 3 hr, the mixture was stored at 4°C overnight with constant stirring. Immediately prior to use, the anti-antithrombin III agarose was washed exhaustively with 1.0 M sodium chloride and then equilibrated in 0.15 M sodium chloride.

Antithrombin III activity was measured by a two-stage amidolytic technique. The assay for activated clotting factors has been described previously. Basically, the test was a standard nonactivated partial thromboplastin time (NAPTT) using nonactivated human platelet-deficient plasma (NHPDP) as substrate. Meticulous care was taken during preparation of this substrate to prevent contact activation and to separate as completely as possible all platelets. Centrolex-P (lecithin, Central Soya, Chicago, Ill.) was used as phospholipid supplement.

*These materials were supplied through the generosity of Dr. Milan Wickerhauser of the American Red Cross National Fractionation Center with the partial support of Grant HE-13881 (HEM) from the National Institutes of Health.
Fig. 1. Standard curve obtained from a factor IX complex standard (Lot K. 5156) used to quantitate activated factors in PCC experiments. The factor IX complex standard was reconstituted at 10 mg/ml, diluted as indicated, and assayed for activated factors. In the example illustrated (see Fig. 2), 78% of the coagulant activity in the control sample (NAPTT 37.0 sec; 78 arbitrary PCC units) was neutralized by SBTI at a final concentration of 0.01 mg/ml (NAPTT 59.2 sec; 17 arbitrary PCC units). A 0.10% (w/v) suspension was prepared by homogenization of the dried soybean extract in 0.15 M sodium chloride. Homogenization was performed at 4°C to prevent oxidation of phospholipid double bonds and to enhance emulsification. This phospholipid supplement was divided into small portions in plastic test tubes and stored at -20°C until use. For the assay, the substrate plasma and the Centrolex-P were thawed and kept at 4°C. Individual assays were performed as follows: 0.1 ml substrate plasma, 0.1 ml Centrolex-P, and 0.1 ml of sample were mixed in a polystyrene tube (10 x 75 mm) and warmed at 37°C for exactly 1 min. Recalcification was accomplished by the addition of 0.1 ml 0.025 M CaCl₂ and the clotting time was recorded. The results are expressed as the average of two determinations in seconds or in arbitrary units derived from a factor IX complex standard (Lot No. K. 5156) obtained from Dr. David Aronson of the Bureau of Biologics (see Fig. 1).

Fibrinogen clotting activity was determined as follows: 0.2 ml of a fibrinogen solution (5 mg/ml in 0.15 M NaCl) was warmed at 37°C for 30 sec; 0.1 ml of the sample was then added and the clotting time determined. This assay detected as little as 0.001 NIH units thrombin per ml.

The experiments were performed in the following manner. The reconstituted prothrombin complex concentrates were mixed in plastic tubes with various test materials. After appropriate periods of incubation at 21°C or 37°C, samples were removed from this reaction mixture, diluted 1:10 (or 1:20) in 0.06 M Tris and 0.09 M NaCl at pH 7.5, and assayed for activated clotting factors or for fibrinogen clotting activity. It was found that there was a critical concentration of the test material in the reaction mixture above which there was significant inhibition of the substrate plasma in the second-stage assay. On each day of experimentation, control experiments were performed to determine this critical concentration. Serial dilutions of the test material were added to reaction mixtures containing buffer instead of PCC. These were incubated and diluted as above and assayed using a kaolin-activated partial thromboplastin time (APTT). The maximal dilution causing no prolongation of the second-stage APTT was used in subsequent experiments.

RESULTS

The two concentrates differed greatly in their clot-promoting activity (Table 1). Marked shortening of the NAPTT of normal human plasma in plastic tubes was observed with the thrombogenic concentrate (Hyland Laboratories),

<table>
<thead>
<tr>
<th>Table 1. Comparison of Clinical Concentrates</th>
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<tr>
<td>Reaction Mixture*</td>
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</tr>
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<tr>
<td>Nonthrombogenic PCC</td>
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<td></td>
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<tr>
<td>Thrombogenic PCC</td>
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*Concentrates reconstituted at 10 mg/ml in distilled water immediately prior to assay. Concentrates then diluted in 0.06 M Tris-0.09 M NaCl and assayed for activated clotting factors.
indicating the presence of significant amounts of potentially thrombogenic material. In comparison, the nonthrombogenic concentrate (American Red Cross) contained little clot-promoting activity, a finding that was related, in part, to the presence of a coagulation inhibitor (which we have previously identified as heparin through the use of bacterial heparinase) and, in part, to deliberate fortification with antithrombin III during the final production step. Little heparin was detected in the thrombogenic concentrate.

Identity of Coagulant Material

Initial studies were based on the assumption that at least some of the clot-promoting materials present in the thrombogenic concentrate were activated clotting factors, probably of the vitamin K complex, some or all of which possessed an active site serine residue. To test this assumption, the following experiments were performed. Antithrombin III, a physiologic inhibitor of the coagulation serine proteases, and heparin, which potentiates the action of antithrombin III, were examined for their ability to neutralize the coagulant material found in the thrombogenic concentrate. The concentrations of heparin and antithrombin III were adjusted so that there was little or no effect of these substances on the substrate plasma. The results of these experiments are shown in Table 2. The addition of heparin at a final concentration of 0.5 unit/ml and antithrombin III at a final concentration of 0.1 mg/ml to the thrombogenic concentrate completely neutralized the coagulant activity. Only partial neutralization occurred when either heparin or antithrombin III were used alone.

Individual enzymes in the thrombogenic concentrate were identified by specific assay and enzyme-inhibition studies. The concentration of thrombin in the reconstituted concentrate as determined by fibrinogen clotting time was less than 0.001 unit/ml. Furthermore, treatment of the concentrate with 0.001 M TLCK at pH 8.0, conditions which have been shown to inactivate thrombin, had no appreciable effect on the coagulant activity. These studies indicated that there was essentially no thrombin in the sample examined. On the other hand, inhibitors of factor Xa had a significant effect on the concentrate in question. SBTI, a specific inhibitor of factor Xa, partially inhibited the coagulant activity of the concentrate (Fig. 2). Similarly, treatment with PMSF at $4 \times 10^{-3}$ M

| Table 2. Effects of Heparin and Antithrombin III (AT III) on the Thrombogenicity of PCC |
|---------------------------------|--------|--------|
| Reaction Mixture*               | Dilution | NAPTT (sec) |
| Thrombogenic PCC                | 1:10 | 47.6/57.1 |
| Thrombogenic PCC                | 1:20 | 56.9/66.1 |
| Thrombogenic PCC + heparin      | 1:10 | 69.3/80.0 |
| Thrombogenic PCC + AT III       | 1:10 | 102.9/116.5 |
| Thrombogenic PCC + heparin + AT III | 1:20 | 139.5/135.5 |
|                                    | >250/>250 |

*Reaction mixture contained 0.5 ml of the concentrate reconstituted at 20 mg/ml, and either 0.1 ml of heparin (5 units/ml), 0.1 ml of antithrombin III (1 mg/ml), or both. The final volume of each mixture was adjusted to 1 ml with 0.05 M Tris, pH 8.0. Assays were performed as described in the text after dilution in buffer.
Fig. 2. Effect of various inhibitors on the coagulant activity of the thrombogenic PCC. The concentrate was reconstituted at 20 mg/ml. The reaction mixture contained 0.5 ml PCC, 0.4 ml buffer, and 0.1 ml of either SBTI (0.1 mg/ml), PMSF (0.04 M), a 1:5 dilution of a factor IX inhibitor (anti-IX), or buffer (control). After incubation at 21°C for 30 min, 0.1 ml was removed, diluted 1:10 in buffer, and assayed for activated factors. In each case, the residual coagulant activity, determined from an arbitrary factor IX complex standard (see Fig. 1), that remained after incubation with the inhibitor is expressed as a percentage of the control coagulant activity.

at pH 8.0, which also inhibits factor Xa, but not factor IXa, resulted in partial inhibition of the coagulant activity (Fig. 2). These studies suggested that factor Xa was, in part, responsible for the clot-promoting activity in vitro. However, it was clear that other factors were involved as well. A high-titer inhibitor from a patient with hemophilia B was used to assess the presence of factor IXa. Again, partial inhibition of the coagulant activity was seen that was similar to that observed with the inhibitors of factor Xa (Fig. 2). Anti-albumin had no discernible effect.

Evolution of Coagulant Material

Having partially defined the coagulant activity of the thrombogenic concentrate, attention was then directed toward clinically relevant factors which might influence the evolution of this activity during production, storage, or infusion of the concentrates. To assess the importance of plasma levels of antithrombin III in persons receiving PCC, the experiments with heparin and antithrombin III were repeated with substrate plasma which had been partially depleted of antithrombin III using an agarose-bound rabbit antiserum against human antithrombin III (Table 3). A 40% increase in the coagulant activity of the throm-
Table 4. Effect of Calcium, Strontium, and Factor XIa on the Thrombogenic Activity of PCC

<table>
<thead>
<tr>
<th>Reaction Mixture*</th>
<th>Incubation Time (min)†</th>
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<tr>
<td>Concentrate A +</td>
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<tr>
<td>CaCl₂</td>
<td>(&gt;50)</td>
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<tr>
<td>Concentrate A +</td>
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<tr>
<td>Sr(OAc)₂</td>
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<tr>
<td>CaCl₂ + XIa</td>
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<tr>
<td>Sr(OAc)₂</td>
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<td>Concentrate B +</td>
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<tr>
<td>Sr(OAc)₂ + XIa</td>
<td>(&gt;50)</td>
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*Reaction mixture contained 1.0 ml of the concentrate reconstituted at 20 mg/ml, 0.2 ml of either 0.05 M CaCl₂ or 0.05 M Sr(OAc)₂, and 0.1 ml of either Factor XIa (0.1 mg/ml) or 0.09 M NaCl-0.06 M Tris, pH 7.4. The final volume was adjusted to 2.0 ml with buffer.
†Samples were incubated at 37°C for 3 hr. At each time interval, 0.1 ml was removed, diluted 1:10 in buffer and assayed using NHPDP (or fibrinogen) as substrate.
†Clotted before addition of CaCl₂.

bogenic concentrate was observed in the depleted plasma (NAPTT, 34.0 sec, 112 arbitrary PCC units, to NAPTT 31.2 sec, 154 arbitrary PCC units). More striking was the finding that the ability of heparin to neutralize the coagulant activity of the concentrate was diminished in the depleted plasma. As before, the addition of both heparin and antithrombin III to the concentrate completely inhibited the activity.

The results of studies examining the effect of divalent cations are summarized in Table 4. In these experiments, each concentrate was incubated in the reaction mixture with either calcium or strontium ions at ambient temperature for periods of time up to 48 hr. Portions of the respective reaction mixtures were removed at various intervals and tested for activity. Incubation with calcium resulted in progressive evolution of additional coagulant activity, even from the concentrate shown previously to have no potentially thrombogenic material in the untreated state. Up to 200 NIH units/ml of thrombin were detected after longer periods of incubation and accounted for much of the additional coagulant activity detected by the NAPTT. The addition of both heparin and antithrombin III to the concentrate completely inhibited the activity.

Because of the known effect of polycations on the conversion of prothrombin to thrombin and the frequent use of polycations (e.g., DEAE-cellulose) in fractionation procedures for the preparation of PCC, the influence of several
Table 5. Effect of Antithrombin III (AT III) and Heparin on the Evolution of Thrombogenic Activity of PCC

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<th>120</th>
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<td>Concentrate B + CaCl₂</td>
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<td>70.2</td>
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<tr>
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<td>184.8</td>
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<td>75.8</td>
<td>44.2</td>
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<td>Concentrate B + CaCl₂ + heparin</td>
<td>158.4</td>
<td>90.6</td>
<td>65.4</td>
<td>51.5</td>
<td>47.0</td>
</tr>
<tr>
<td>Concentrate B + CaCl₂ + AT III + heparin</td>
<td>171.3</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
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*Reaction mixture contained 0.5 ml of the concentrate reconstituted at 20 mg/ml, 0.1 ml of 0.05 M CaCl₂, and either 0.1 ml heparin (5 units/ml) or 0.1 ml antithrombin III (1 mg/ml), or both. The final volume was adjusted to 1 ml with buffer.

†Reaction mixtures were incubated at 21°C. At each time interval, 0.1 ml was removed, diluted 1:10 with buffer, and assayed as described in the text.

of these compounds on the evolution of coagulant activity was also studied (Fig. 3). At a final concentration of 10 mg/ml, DEAE-cellulose generated large amounts of coagulant activity from the nonthrombogenic concentrate but none from normal plasma. This coagulant activity evolved over a period of 24 hr during incubation with DEAE-cellulose and occurred in the absence of exogenous calcium or phospholipid. No thrombin was detected. When polylysine was used instead of DEAE-cellulose, much larger quantities of coagulant material were observed, again in the absence of exogenous calcium and phospholipid.

Fig. 3. Time course of the evolution of coagulant activity from the nonthrombogenic PCC in the presence of poly-L-lysine (PLL) or DEAE-cellulose (DEAE). The PCC was reconstituted at 20 mg/ml in both experiments. In experiments with PLL, the reaction mixture contained 1.0 ml of NHPDP (·) or PCC (·) and 0.2 ml PLL (10 mg/ml). The final volume was adjusted to 2.0 ml with buffer. The experiments with DEAE-cellulose were performed with reaction mixtures containing 2.0 ml NHPDP (×) or PCC (×) and 20 mg DEAE-cellulose. All samples were incubated at 21°C for 24 hr. At each time interval, 0.1 ml was removed (after centrifugation in the case of DEAE-cellulose), diluted 1:10 in buffer, and assayed. The results are expressed in terms of an arbitrary factor IX complex standard (see Fig. 1).
DISCUSSION

The potentially lethal hypercoagulable state that attends the use of PCC is attributed to potent coagulant materials present in the concentrates. The following evidence links this material to the hypercoagulable state:14,24 (1) Unaltered PCC greatly accelerates the clotting time of normal plasma as well as plasmas deficient in factors IX, VIII, or X. This result is analogous to the effect of serum on plasma and indicates the presence in the respective concentrate of an activated component or components not found in plasma. (2) Statistically, there is a close correlation between the amount of this material in a given concentrate as determined in vitro by the NAPTT and the thrombogenicity of that concentrate in an animal model in vivo. (3) Finally, clinical anecdotes of thrombosis in man correlate roughly with the thrombogenicity in vitro of a given concentrate.

In the present study, two concentrates, each with markedly different coagulant activity, have been examined. The coagulant material in the thrombogenic concentrate is heterogeneous and consists of several activated clotting factors of the intrinsic system, principally factors Xa and IXa. This conclusion is based primarily on the pattern of inhibition observed with various enzyme inhibitors. The possibility that other coagulant enzymes are present in this or other PCC is difficult to assess at this time. Thrombin could not be detected by highly sensitive assay techniques. Factor VIIa, which can be formed by the proteolytic action of either factor Xa or thrombin, but which requires tissue factor for its expression,38 has not been assayed directly. Factor VIIa is inactivated by heparin and antithrombin III,39 so it is possible that small amounts of factor VIIa are present in PCC. It is also possible that other factors in the intrinsic system might be present. The slight increase in coagulant activity in the thrombogenic concentrate that occurs upon incubation with strontium ions is consistent with the presence of traces of factors of the contact phase of blood coagulation.40

Although enzymatically active material has not been detected in the non-thrombogenic concentrate, it is possible to convert this preparation to a potentially thrombogenic one by several manipulations, including incubation with calcium or activated factor IX. These manipulations result in the evolution of large amounts of coagulant activity, particularly thrombin, from the thrombogenic concentrate. Similar findings have been described by Sas et al. and have been used to estimate the potential thrombogenicity of PCC.41 The importance of these findings are twofold. First, they suggest that even PCC which contain no detectable coagulant activity might be thrombogenic in vivo under certain conditions of infusion. For example, concomitant administration of calcium-containing fluids, such as Ringer's lactate, might lead to the evolution of potentially thrombogenic material. Second, they show that while thrombin generation may well correlate with the thrombogenicity of a given concentrate, there are some concentrates that may evolve no detectable thrombin but which nevertheless contain potent coagulant enzymes and may be thrombogenic in vivo. This effect is particularly true of some concentrates that contain large amounts of heparin.
Significant coagulant activity is also generated during incubation with DEAE-cellulose, a material which is frequently used in the preparation of PCC. This finding and the similar observation with calcium, which is present in hydroxyapatite, another commonly used adsorbent in the preparation of PCC, suggest mechanisms by which the active enzymes in the final product might be generated. Calcium, of course, plays an important role in a number of coagulation reactions and, in the presence of trace quantities of activated factors, might permit the generation of large amounts of potentially thrombogenic activity. The mechanism by which DEAE-cellulose generates such activity is less obvious, but might occur by methods analogous to those proposed for the catalytic activity of polylysine. In the presence of factor Xa, polylysine catalyzes the conversion of prothrombin to thrombin, perhaps by substituting for calcium ions and factor V. Polylysine also appears to convert factor X to factor Xa. DEAE-cellulose may act like polylysine in one or both of these reactions and thereby generate coagulant activity from PCC. Alternatively, DEAE-cellulose may remove certain naturally occurring protease inhibitors, like antithrombin III, from the concentrates, thus permitting the generation of coagulant activity.

Finally, the possible role of the extrinsic pathway in generating coagulant activity during preparation of PCC deserves mention. Current evidence suggests that factor VII is recovered from plasma in a partially active form which, in the presence of tissue factor and calcium, activates factor X. Minute quantities of factor Xa generate a fully active form of factor VII by feedback mechanisms which will in turn generate more factor Xa. Feedback reactions of factor Xa on other factors of the intrinsic pathway may also be important in the generation of coagulant activity in PCC.

Although the precise mechanism underlying the evolution of coagulation activity in PCC is uncertain, these results do show that antithrombin III, along with heparin, is a powerful modifying influence on the potential thrombogenicity of a given concentrate. Recent observations by Rosenberg suggest that several of the proteases which are present or can be induced in PCC are rapidly and irreversibly neutralized by antithrombin III and that the rate of neutralization can be markedly accelerated by heparin.

Therapeutically, antithrombin III might be used in several ways to decrease the thrombotic risk from PCC. Fortification of the concentrates at various stages during production might inhibit the thrombogenic enzymes and reduce the risk of thrombosis. We have detected far less enzymatic activity in the Red Cross concentrate, one which had been pretreated with antithrombin III and heparin, than in a concentrate which had not been so treated. Furthermore, the presence of antithrombin III and heparin prevent the generation of activated factors that occurs during incubation with calcium. These findings suggest that the addition of heparin and antithrombin III early in the production process can significantly inhibit the evolution of coagulant activity. In addition, the results show that the thrombogenicity of the concentrates can be significantly modified by the addition of heparin and antithrombin III at much later steps, even after reconstitution of the lyophilized material. The most likely explanation for our previous inability to relate the PCC antithrombin III
levels to the thrombogenic potential is that either the levels of antithrombin III present in most concentrates are insufficient to neutralize activated enzymes or the antithrombin III detected immunologically in PCC is already enzyme bound and therefore unavailable.

Another method of reducing the thrombotic risk of PCC might be augmentation of host levels of antithrombin III. The evidence that recipient antithrombin III levels may be important in determining the thrombogenic potential of administered PCC is as follows. Families congenitally deficient in antithrombin III experience a high incidence of venous thrombosis. Decreased levels of antithrombin III have also been reported in certain acquired hypercoagulable states such as diffuse intravascular coagulation and liver disease. The latter group is especially noteworthy since they comprise a small group that is unusually susceptible to the thrombogenic materials in PCC. It has previously been speculated that decreased levels of antithrombin III in these patients may partially explain this increased risk of thrombosis. In the present study, a situation analogous to those described above has been created in vitro by depletion of substrate plasma of antithrombin III. These depleted plasmas are found to be more sensitive to the thrombogenic enzymes in PCC than were plasmas containing normal amounts of antithrombin III. Furthermore, the ability of heparin to neutralize the coagulant activity present in the concentrate studied is impaired when assayed in the depleted plasma.

These studies provide support for the recommendation that PCC be tested routinely for the presence of activated factors prior to use and that the clinical use of concentrates containing these activated factors be limited to patients in whom the need for therapy clearly outweighs the thrombotic and other risks. Several potential approaches to modifying the effects of activated clotting factors in PCC have been explored. The possibility that any or all of these procedures can decrease the thrombotic risk of PCC warrants further investigation.

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PROTHROMBIN COMPLEX CONCENTRATES

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Prothrombin complex concentrates: potentially thrombogenic materials and clues to the mechanism of thrombosis in vivo

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