The Role of the Liver in Serum-induced Hypercoagulability *

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The infusion of normal human serum into animals engenders a transient period of hypercoagulability characterized by profound shortening of the whole blood clotting time in both glass and silicone-coated tubes (2). During this period of hypercoagulability, blood trapped in isolated venous segments rapidly coagulates, forming a thrombotic cast of the isolated venous segment (3). In previous experiments it has been demonstrated that the ability of serum to induce thrombosis in the recipient animal is dependent on the presence of activated coagulation Factors IX (plasma thromboplastin component) and XI (plasma thromboplastin antecedent) in the infused serum (4). It was suggested that the presence of activated Factor XI was essential for the activation of Factor IX, and that activated Factor IX accelerated a rate-limiting step in the coagulation mechanism in the recipient animal to a degree that exceeded the capacity of a postulated cellular clearance mechanism, similar to that previously demonstrated in the rat by Spaet (5).

In the present study the duration of the hypercoagulability produced by the infusion of serum was examined in the intact rabbit by measuring thrombus formation in venous segments isolated immediately and at intervals after serum infusion. These experiments demonstrate that in the intact animal the liver plays a central role in the attenuation of serum-induced hypercoagulability, as had been suggested by initial experiments of Wessler and associates (6). Further studies indicate that the isolated rabbit liver, perfused in situ, is capable of removing the capacity of the perfused serum to induce hypercoagulability. The attenuation of the capacity of serum to induce hypercoagulability was found to occur in association with reduction in the levels of activated coagulation Factors IX and XI in the perfused serum.

Methods

A) Collection of serum. Human serum was collected by venipuncture, using silicone-coated syringes and needles, with a two-syringe technique. The blood was immediately transferred to new uncoated glass tubes before coagulation ensued. Serum samples were allowed to stand for 2 hours at room temperature and then for 18 hours at 4°C. They were subsequently centrifuged for 20 minutes at 2,500 × g, and the serum was removed. The serum used for the clearance studies in the intact animal was collected from a pool of five donors. Portions of the pooled serum were stored at −20°C and were thawed immediately before infusion. The serum used for perfusion studies was obtained from individual donors the day before the perfusion and was perfused immediately after the 18-hour storage period at 4°C.

B) Thrombosis assay. Thrombus formation was measured by a standard rabbit assay (7). Male New Zealand white rabbits ranging in weight from 1 to 3 kg were used in all experiments. The rabbits were anesthetized with intravenous sodium pentobarbital. On each side of the neck a 1- to 2-cm length of external jugular vein was freed from its surrounding structures, and its major tributaries ligated. Human serum was infused at a fixed dose of 1.32 ml per kg. Before infusion, serum was warmed to 37°C and diluted to a final volume of 5 ml with isotonic saline. All infusions were performed with siliconized syringes and needles. In the standard assay, serum was infused into the marginal ear vein of the rabbit over a period of 15 seconds. After a further interval of 15 seconds (30 seconds from the beginning of the infusion), the previously freed venous segments were isolated from the circulation with silk ligatures. After 10 minutes, one of the segments was excised and opened into a petri dish containing 5% sodium citrate. After 15 minutes the second segment was excised and

* Submitted for publication August 13, 1965; accepted November 8, 1965.

Supported by U. S. Public Health Service research grant HE-06316 from the National Heart Institute, and by grants-in-aid from the William F. Milton Fund, Harvard Medical School, and from the Massachusetts Heart Association.

Presented in part at the meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 1965 (1).

† Recipient of a Career Development Award from the National Heart Institute, Bethesda, Md.

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opened in a similar fashion. The amounts of thrombus formed were scored on a scale ranging from 0 to 4: a score of 0 represented no thrombus formation; a score of 1, a few macroscopic strands of fibrin; a score of 2, several small thrombi; a score of 3, two or more large thrombus fragments; and a score of 4 represented a single thrombus forming a cast of the isolated venous segment. At the standard dose of 1.32 ml of normal glass-contacted human serum per kilogram, 100% of test rabbits in this study developed a score 4 thrombus within 10 minutes of stasis. In contrast, infusions of saline routinely failed to produce thrombosis in the isolated venous segments.

In several experiments the standard bioassay was modified. In some the interval of stasis within the segment was prolonged beyond 10 and 15 minutes. In others the interval between the completion of the infusion and the isolation of the segment from the circulation was prolonged beyond 15 seconds, and in other experiments both the delay in isolation of the segments and the duration of stasis were altered simultaneously. In addition, other sites of infusion were employed, including the femoral and portal veins. When infusions were made through the portal vein, its major tributaries were ligated before infusion to insure passage of serum through the liver. The dose of serum remained fixed at 1.52 ml per kg in all instances, and the external jugular veins were always isolated for the detection of thrombosis.

C) In vitro clotting tests. Activated Factor XI (activation product), Factor VII (convertin)-X (Stuart) complex, and Factor X activities were measured as previously described (4). Factor IX activity in serum was measured by a modification of a previously described technique (4). The assay utilized as a substrate hen plasma, devoid of Factors IX, XI, and XII (Hageman) to which was added an activated Factor XI concentrate prepared from human plasma by the technique of Waaler (8). Normal human plasma was stirred with Speedex 1 (125 mg per ml) at 23°C for 30 minutes. The Speedex was separated from the plasma by centrifugation at 12,500 X g for 10 minutes, and the supernatant plasma was discarded. The Speedex was washed three times with 0.85% NaCl. Activated Factor XI was eluted from the Speedex with 7% NaCl (using one-fifth the original volume of plasma). The Factor XI-rich eluate was then dialyzed exhaustively against 0.85% NaCl. Although there was usually no measurable coagulation factor activity other than Factor XI and XII in the preparation, occasional traces of thrombic activity were found. To remove the thrombin contamination, we raised the pH of the preparation to 11 by the addition of 0.1 N NaOH, and incubated the fraction at 25°C for 30 minutes, after which the pH was restored at 7.35 with 0.1 N HCl. This sequence was repeated until no thrombic activity could be detected. The Factor IX assay was performed with dilution fluid II of Waaler (8) as diluent by adding to a siliconized tube in order: 0.1 ml of the test serum diluted 1:10; 0.1 ml Factor XI concentrate; and 0.1 ml of commercial partial thromboplastin* diluted 1:10. Reagents were added at melting-ice temperature and were incubated at 37°C for 30 seconds, after which 0.1 ml of hen plasma, diluted 1:2 was added and the incubation continued for an additional 30 seconds. Finally, 0.1 ml of 30 mM calcium chloride was added and a stop watch started. The tube was allowed to stand for 30 seconds and was then gently agitated every 5 seconds until a firm coagulum developed, at which time the clotting time was recorded. Calibration curves were prepared daily.

Thrombic activity was measured by the technique of Johnson and Seegers (9).

D) Liver perfusion technique. In situ rabbit liver perfusions were performed by a method adapted from Spaet (5). A midline abdominal incision was made in anesthetized rabbits weighing 0.75 to 1.0 kg, and the portal vein and inferior vena cava were dissected free. The superior mesenteric vein, a tributary of the portal vein, was ligated. Isotonic saline, warmed to 37°C, was perfused into the portal vein through siliconized tubing and a siliconized needle driven by a peristaltic pump a at a rate of 30 ml per minute. The inferior vena cava was ligated above the diaphragm, and effluent flow was collected from a catheter placed in the inferior vena cava at a level above the entrance of the renal veins. After 10 minutes of saline infusion, human serum was placed in a siliconized, water-jacketed reservoir maintained at 37°C placed at a level 15 cm below the liver. Saline perfusion was discontinued and serum infusion instituted. Flow from the effluent catheter, after an initial 30 ml of serum had been perfused through the liver, was returned directly to the reservoir by gravity. Samples to be assayed for Factor XI, X, IX, and VII activity, as well as for thrombic activity in rabbits, were taken from the reservoir before and at intervals during the perfusion. Activity of each coagulation factor was referred to a calibration curve constructed by serial dilution of the starting serum.

The viability of the liver preparation during the 40 minutes of perfusion was examined in four experiments by measuring the release of serum glutamic oxaloacetic transaminase activity (10) into the perfused serum. The initial activity was 30.0 ± 8.6 U; after 40 minutes of perfusion, the activity was 27.0 ± 8.4 U. In a separate series of experiments, the rates of clearance of Bromsulphalein (BSP) were examined. The initial rate of BSP clearance was examined by adding 5 mg of BSP to 100 ml of 0.85% sodium chloride and then perfusing through an isolated liver. In four perfusions the BSP was

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1 Dicalite Speedex, Great Lakes Carbon Co., Walteria, Calif.
2 Thromboplast reagent, Ortho Research Laboratory, Raritan, N. J. Supplied through the courtesy of Dr. Heron Singer.
4 These determinations were performed by Mr. Murray Golub, Clinical Chemist, Beth Israel Hospital, Boston, Mass.
5 Mean ± SE.
concentration was reduced to 10.4 ± 2.8% of the initial level at 10 minutes. In a second series of four experiments, the BSP-containing saline was perfused after an initial 40-minute perfusion with saline alone. The BSP concentration was reduced to 10.6 ± 2.7% of the initial value at 10 minutes (50 minutes after the onset of saline perfusion).

These studies indicate that the liver maintained its metabolic viability (as measured by BSP clearance) and cellular integrity (as measured by release of serum glucotonic oxaloacetic transaminase activity) for the 40 minutes of perfusion.

Results

A) Clearance of serum-induced hypercoagulability in the intact animal. An investigation of the duration of the thrombotic response to serum in the intact animal was undertaken by altering two of the components of the standard bioassay. In all instances, the usual dose of serum (1.32 ml per kg) was infused over a period of 15 seconds. The interval between completion of the infusion and isolation of the venous segment was progressively prolonged from an initial delay of 15 seconds to a maximum of 30 minutes. In addition, the duration of stasis within the segment before opening the segment to examine for the presence of thrombus was varied from 10 minutes to 60 minutes (Table I). When the duration of stasis within the isolated segment was 10 minutes, a complete thrombus (score 4) was routinely observed when the interval of time between the completion of the infusion and isolation of the segment was 15 or 30 seconds. After 30 seconds, however, progressively fewer complete score 4 thrombi were observed, and after a delay of 120 seconds, no thrombi were observed at 10 minutes of stasis. When the stasis within the segment was prolonged beyond 10 minutes, however, thrombosis was observed at progressively longer intervals after completion of the infusion. Thus, at 180 seconds of delay before segment isolation, no thrombosis was observed if stasis was continued for 10 or 15 minutes, whereas partial thrombi were observed if stasis was continued...
continued for 20 minutes, and by 40 minutes of stasis complete thrombosis occurred in all segments examined. Indeed, if stasis was prolonged for 60 minutes, complete thrombosis occurred even when the interval of time between the completion of the serum infusion and the isolation of a segment was as long as 30 minutes. Control experiments, in which saline infusions replaced serum infusions, were routinely negative (score 0) over the entire range of stasis examined. These findings indicate that the thrombotic response to infused serum is markedly attenuated after infusion, but that if stasis is permitted to continue for a sufficient period of time, evidences of hypercoagulability persist for as long as 30 minutes.

To examine the specificity of the site of infusion of serum into the venous circulation, comparable experiments were undertaken in which the serum was infused into the femoral vein rather than into the marginal ear vein. No significant difference in the pattern of clearance of the serum-induced thrombotic response was detected under these circumstances. In striking contrast were the results of infusions of serum into the portal vein (Table II). Whereas in both the ear vein and femoral vein infusions thrombosis was uniformly present when the segment was isolated 15 seconds after the infusion, and stasis continued for 10 minutes when serum was infused into the portal vein, only partial thrombosis was observed under similar conditions. After 45 seconds of delay before the isolation of the segment, only 15 minutes of stasis was required for a complete thrombus to form when serum was infused via the marginal ear vein (Table I). After a delay of 45 seconds after infusion into the portal vein, however, 40 minutes of stasis was required to elicit complete thrombosis (Table II). These findings indicate a striking acceleration of the attenuation of the thrombosis-inducing capacity of serum when the serum was initially perfused through the liver, although the thrombogenic activity was not completely removed.

Additional experiments were performed in which the hepatic artery and vein were occluded during the interval of delay before the segment was isolated. The marginal ear vein was the site of infusion. Comparable experiments were also performed in which the renal arteries and veins were clamped during the interval between completion of the infusion and isolation of the segment (Table III). In the absence of circulation through the liver (Table III, line A), the thrombogenic response to infused serum persists unaltered. In all animals in which the liver was excluded from the circulation after the infusion of human serum, death occurred within 15 minutes. Autopsy examination of these animals revealed massive thrombosis in the major arteries and veins, including the heart’s blood. In control experiments in which saline was infused rather than serum, occlusion of the hepatic circulation did not result in thrombosis in any isolated segment, even when stasis was protracted for 60 minutes. In these animals, autopsy examination revealed no thrombosis in any major vessel. In the presence of occlusion of the renal circulation (Table III, line B), clearance of the thrombotic response to infused serum was similar to that observed in the presence of an intact renal circulation.

### TABLE III

| Time of Injection (minutes) | Rabbits with thrombi scored
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>-----------------------------</td>
<td>----------------------------</td>
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<table>
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<th>A. Hepatic artery and portal vein occluded until segment isolated</th>
<th>0 0 0 0 5</th>
<th>0 0 0 0 5</th>
<th>0 0 0 0 5</th>
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</thead>
<tbody>
<tr>
<td>B. Renal arteries and veins occluded until isolation of segment</td>
<td>0 0 0 3</td>
<td>0 1 1 1</td>
<td>0 1 2 0</td>
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</table>

* Delay, in seconds, before segment isolation. Human serum (1.52 ml per kg) infused into the marginal ear vein.
† Bioassay score as in Table I.
‡ Duration of stasis in isolated venous segments = 10 minutes.
TABLE IV
Coagulation factor activity and thrombosis assays in human serum

<table>
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<tr>
<th>Minutes of perfusion</th>
<th>VII*</th>
<th>X</th>
<th>XI</th>
<th>IX</th>
<th>No. of assays at bioassay score*</th>
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<td>100</td>
<td>100</td>
<td>100</td>
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<td>96 ± 2.8</td>
<td>85 ± 5.9</td>
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<td>84 ± 4.7</td>
<td>125 ± 45</td>
<td>33 ± 3.3</td>
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<td>94 ± 3.1</td>
<td>84 ± 4.3</td>
<td>109 ± 16</td>
<td>21 ± 2.7</td>
<td>1 1 3 0 3</td>
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<tr>
<td>30</td>
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<td>84 ± 5.0</td>
<td>40 ± 12</td>
<td>13 ± 2.2</td>
<td>4 2 1 0 1</td>
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<tr>
<td>40</td>
<td>88 ± 2.9</td>
<td>74 ± 5.0</td>
<td>13 ± 6.2</td>
<td>11 ± 2.0</td>
<td>7 1 0 0 0</td>
</tr>
</tbody>
</table>

* Coagulation factors are expressed as per cent initial activity. Mean of eight perfusions ± standard error of the mean.
† Bioassay score as in Table I. Duration of stasis = 10 minutes. One bioassay sample lost at 5 minutes and another at 10 minutes of perfusion.

In a separate group of three animals, hepatic occlusion was established immediately after the infusion of serum. Five minutes after the serum infusion, 50 mg of heparin was injected intravenously. In contrast to the nonheparinized animals, all the rabbits survived. They were sacrificed at 30 minutes, and autopsy examination revealed thrombosis of the hepatic artery and of the portal and mesenteric veins, but not in the general circulation.

B) Liver perfusion studies. To study further the mechanism by which the liver participates in the clearance mechanism, a series of in situ liver perfusions was performed. Human serum was perfused through rabbit livers for 40 minutes. Samples were removed from the reservoir at intervals before and during the perfusion and were analyzed for Factor VII, IX, X, and XI activities and for serum thrombosis-inducing capacity by the standard bioassay technique. Data from eight perfusions are presented in Table IV. Factor IX was efficiently cleared by the liver, whereas Factors VII and X were minimally altered. In some perfusions paradoxical initial rises in the level of Factor XI were observed, but in all perfusions the level of Factor XI was eventually markedly reduced. An impairment of the thrombosis-inducing capacity of serum became progressively evident in all perfusions. It was not possible to correlate directly the observed impairment with a specific level of either Factor XI or IX, although a temporal correlation between the depression of Factor IX and loss of thrombogenic activity was apparent. In a control perfusion in which the serum was perfused through the tubing and reservoir only, after 40 minutes the clotting factor activities (expressed as per cent initial activity) were these: VII, 100%; IX, 78%; X, 93%; and XI, 97%. The thrombosis-inducing capacity of the serum was not altered during the control perfusion.

In an effort to exclude the possibility that the observed changes in the coagulation factors and in the thrombogenic capacity of serum during perfusion through the liver reflected the release of heparin into the perfusate, we incubated samples from one perfusion with thrombin and fibrinogen (Table V). No antithrombic activity was present. In this system as little as 0.1 U of heparin added to the serum produced pronounced prolongation of the clotting time. To examine whether the attenuation of clotting factor activity and of the thrombotic capacity of serum resulted from release of an inhibitor into the perfusing medium, we undertook studies in which samples

* Complete system contains: 0.3 ml Johnson-Seegers barbital-acacia buffer, 0.1 ml serum, 0.1 ml thrombin, and 0.1 ml bovine fibrinogen (15 mg per ml).
† Diluted in isotonic saline.
‡ 0.1 ml saline replaces serum sample.
of the perfusate removed from the reservoir at 40 minutes were mixed in varying proportions with samples taken from the reservoir before perfusion. No inhibitory effect was demonstrable by these mixing studies. In another study saline was perfused through a liver for 40 minutes. Serum samples were diluted 1:10 with the saline obtained at the outset and conclusion of the perfusion, and coagulation Factor VII, IX, X, and XI activities were measured in both diluted sera. No inhibitory activity was detected in perfused saline. Similarly, the perfused saline did not alter the thrombosis-inducing capacity of normal, unperfused serum. These findings indicate that the reduction in levels of Factors IX and XI and the attenuation of thrombosis-inducing capacity of serum did not reflect either the release of heparin into the perfusion medium or the release of a nonheparin inhibitor.

Discussion

The clearance of activated procoagulants from the circulation was first demonstrated by Spaet and Kropatkin in 1958 (11). They demonstrated that intravenously injected soluble blood thromboplastin precursors were ineffective in producing the defibrination syndrome, and they suggested that a cellular clearance mechanism might be operative in the removal of active procoagulants. In subsequent studies Spaet and his associates (5, 12) demonstrated that the reticuloendothelial system removes particulate blood thromboplastin, and that the liver removes soluble blood coagulation product I through a mechanism not dependent on the reticuloendothelial system. In contrast, a recent study by Iatridis, Iatridis, and Ferguson (13) failed to demonstrate the participation of the liver in the clearance of an active procoagulant similar in characteristics to activated Factor XI. These investigators suggest that the attenuation of the thrombotic response after the infusion of Factor XI reflects the presence of a plasma inhibitor and that cellular mechanisms are less important. The findings reported in this communication are consonant with Spaet’s experiments and similarly suggest the direct participation of the liver in the removal of the serum-induced hypercoagulability.

The data presented in Table I indicate that the thrombotic response resulting from the infusion of human serum into rabbits is rapidly dissipated in the intact animal. This observation is qualified by the finding that evidence of the induced hypercoagulable state persists for at least 30 minutes after the infusion, since thrombosis can still be recognized if the duration of stasis is sufficiently prolonged. That the liver plays a key role in the attenuation of the hypercoagulable state is demonstrated by the finding that the infusion of serum directly into the portal vein is far less efficient in producing thrombosis, and that the disappearance of the thrombotic response is far more rapid than when the serum is infused into the marginal ear vein (Table II). In addition, the prolongation of the thrombotic response to serum when the hepatic circulation is occluded (Table III) substantiates the central position of the liver in the removal of the thrombotic stimulus. The importance of the hepatic clearance mechanism is further emphasized by the observation that when the circulation to the liver was occluded the rabbits routinely died within 15 minutes. The observation that death could be prevented by administration of heparin suggests that the death was due to widespread intravascular thrombosis.

Direct participation of the liver in the clearance of serum-induced hypercoagulability was demonstrated by the liver perfusion experiments. During the perfusion of serum through the isolated rabbit liver in situ, Factor IX and XI activities were reduced to low levels (Table IV), and the thrombogenic activity of the serum was similarly depressed. It was not possible to define a specific level of either coagulation activity below which no thrombosis was observed, although a temporal association between Factor IX depression and loss of thrombogenesis was suggested.

The mechanism whereby the liver attenuates a thrombotic response to serum has not been established by these experiments. The absence of a detectable inhibitor in the perfusate suggests that the release of some moiety that preferentially inhibits Factors IX and XI and the thrombogenic activity of serum is not likely.

The clearance of Factor IX and little or no clearance of Factors VII and X by rat livers perfused with serum has been previously demonstrated by Spaet (5). In addition, he reported that addition of protamine diminished the clearance of intermediary blood coagulation product I.
the basis of this observation, Spaet suggested that heparin might play a role in product I inactivation. Because of these observations and because the appearance of heparin in the serum perfusate might preferentially interfere with in vitro assays of Factors IX and XI, rather than those of Factors VII and X, a direct effort was made to detect heparin in the perfusate by seeking evidence of inhibition of thrombin-fibrinogen interaction (Table V). No evidence of heparin release could be detected. These findings do not exclude, however, a binding of these procoagulants with heparin within the liver itself.

The contribution of organs other than the circulating blood and blood vessels has not been sufficiently emphasized in clinical assessment of the "hypercoagulable state." The major function of the liver has been thought to be solely that of procoagulant synthesis. Data presented in this study suggest that in addition to its function in synthesizing blood coagulation factors, the liver plays a central role in the removal of activated procoagulants as well. Indeed, failure in defining the aberrations present in those patients who manifest repeated bouts of thrombophlebitis may reflect an undue emphasis on circulating activated blood coagulation factors, rather than on the homeostatic forces that govern their dissipation.

The importance of vascular stasis in the etiology of clinical intravascular thrombosis has been entrenched since the time of Virchow. Previous experiments have emphasized the role of activated Factors IX and XI in the production of serum-induced thrombosis (4), and the present study indicates that the liver is capable of rapidly removing both activated Factors IX and XI from the circulation. In columns of static blood, however, the defense mechanisms operative in the general circulation may not be effective. Thus, a stimulus capable of activating the blood coagulation sequence locally might be unimpeded by the remote clearance systems if the stasis were sufficiently prolonged. Similarly, activated procoagulants arising in a distant site, on entering an area of retarded blood flow, may have sufficient time to trigger a local thrombotic occlusion, whereas in areas of rapid flow they would be promptly dissipated. Vascular stasis could be viewed as a permissive factor that allows the development of thrombosis in response to a stimulus, arising either locally or from distant areas that would otherwise have been rendered ineffective by rapid blood flow through organs capable of clearing activated procoagulants from the circulation. Although activated Factor IX has been demonstrated capable of inducing thrombosis in areas of vascular stasis in experimental animals, the question that remains unanswered is the nature of those stimuli capable of provoking venous thrombosis in areas of retarded flow in man.

**Summary**

1) In the intact animal, the hypercoagulable state engendered by the infusion of thrombin-free normal human serum is rapidly attenuated.

2) Infusion of the serum through the portal vein, rather than through the marginal ear vein, accelerates the rate of attenuation of the hypercoagulable response to the infused serum.

3) Occlusion of the hepatic circulation after the injection of serum prolongs the hypercoagulable state, and widespread thrombosis occurs in areas of vascular stasis.

4) The perfused rabbit liver is capable of clearing the thrombogenic activity of normal human serum. This clearance occurs in association with the removal of activated Factors IX and XI from the perfusate. No evidence for heparin release or for the appearance of a hepatic inhibitor could be detected.

5) These findings emphasize the importance of cellular mechanisms in the attenuation of serum-induced hypercoagulability.

**References**


HEPATIC CLEARANCE OF SERUM-INDUCED HYPERCOAGULABILITY


