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ABSTRACTS OF PAPERS AND DISCUSSION

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Studies on the In Vivo Preservation of Blood Fluidity

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In the living animal, circulating blood contains all components needed for efficient blood coagulation. Recent studies have greatly clarified the mechanism whereby coagulation is activated in the process of hemostasis; considerably less is known concerning the control of this potentially explosive system so that massive clotting normally is prevented. It is traditionally accepted that initiation of clotting does not occur to any great extent in the presence of normal vascular endothelium, and that naturally present circulating anticoagulants neutralize any slight clotting activity which may develop. However, the degree of protection against the generalized clotting found in experimental animals given potent intravenous coagulants would appear to demonstrate that an additional mechanism of far greater efficiency exists.[1] In animals given intravenous serum there is no precipitation of widespread clotting, but their blood will clot rapidly if it is held stagnant in an isolated vein segment.[2] Findings of this type suggested the hypothesis that circulating blood was prevented from clotting because coagulant activity was cleared upon passage through certain organs or tissues. We have attempted to evaluate this hypothesis by studying the *in vivo* behavior of certain recognizable blood coagulation intermediates.

Blood thromboplastin was that produced by the thromboplastin generation test (thromboplastin generation test reagent = TGTR) or a reagent sedimented on "cephalin" which showed similar clotting properties (sedimented blood thromboplastin reagent = SBTR).[3] Four separate lines of evidence indicated that isologous blood thromboplastin given intravenously to the rat was cleared by the reticulo-endothelial system.

1. When TGTR was injected into the jugular vein or into the aorta, rapid defibrination occurred. When the same reagent was administered via the portal circulation, the degree of defibrination was strikingly reduced.

2. Reticulo-endothelial blockade by means of Gunther-Wagner ink greatly decreased the protective effect of portal injection as compared to systemic injection.

3. SBTR was prepared with P^{32}-labeled "cephalin" obtained from the brains of rats given radioactive sodium orthophosphate. Either crude cephalin or chromatographically purified ethanolamine and serine phosphatides were used with similar results. Following intravenous injection the labeled SBTR was found to have an organ distribution similar to that of agents known to be taken up by the reticulo-endothelial system, the great majority appearing in the liver.

4. Injection of SBTR during the course of a carbon clearance produced significant depression of the carbon clearance curve.

Preliminary data suggest that a similar mechanism is involved in the clearance of an earlier coagulation intermediate. Product I[4] is a term used to designate the clotting activity that develops when adsorbed plasma and serum reagents react in the presence of calcium ion. Intravenous injection of product I into rabbits produced a marked shortening of the plastic tube clotting time[5], which returned to normal in a few minutes. Injection of product I was not followed by defibrination. Since product I was only slowly inactivated by rabbit plasma *in vitro*, *in vivo* clearance is suggested. In rats, ligation of the portal circulation during product I injection produced greater liability to defibrination.

Our studies suggest that the clotting reagents obtained in the laboratory are cleared from the circulation by the reticulo-endothelial system. Although it has not been established that physiological coagulants behave in a similar manner, it is tempting to speculate that clearance of coagulation intermediates is a homeostatic process of fundamental importance in the preservation of *in vivo* blood fluidity. If this hypothesis is confirmed, it will provide a rational explanation for the observation that, within broad limits of tolerance, circulating blood does not clot.

DISCUSSION

PHILIP ROSENBLATT: Years ago I worked with heparin in the course of studying bacterial endocarditis and used heparin quite extensively intravenously. We found, as did others before us and I am sure others have subsequently, that when heparin is given intravenously there is decreased coagulability of the blood as determined by the coagulation time, but, as one graphs this out over a period of time, that not infrequently there is a diminution in blood coagulability, followed by a sharp drop, and this drop not infrequently overshoots the norm, so that it goes into a phase known as increased coagulability. This has been clinically evidenced by the findings of thromboses that may occur in the course of heparin therapy. Now these thromboses do not necessarily occur in any one location where one can implicate the fact of stasis. How would you explain that?

DR. SPAET: First of all, I think that any studies claiming hypercoagulability of the blood must be looked upon with skepticism. I say this with all due respect. One investigator after another has been attempting to demonstrate hypercoagulability, but most coagulationists are still agreed that at present there is no suitable technique. The clotting time methods used to study the effect of heparin are extremely tricky tests, and have failed in the hands of many highly capable laboratory workers either to predict the thrombotic state or to detect more active coagulation.

Now, as to the development of thrombi following heparin therapy, I think that, rather than looking at it as a rebound phenomenon, one must remember that the patients being treated with heparin are patients who have developed thrombi in the first place. I would propose that the reason they developed thrombi was that they had vascular lesions suitable for the laying down first of platelets, and then of the subsequent thrombotic components. Possibly such sites of vascular damage are present in widespread areas. Thus, the original thrombotic state has again been restored by the withdrawal of anticoagulant therapy.

PHILIP ROSENBLATT: Would you apply the same concept of a fundamental vascular lesion of thrombophilia that we see in certain varieties of neoplastic diseases to that which we see in certain patients who are pregnant?

DR. SPAET: The most recent work on this subject is that of a Japanese investigator named Ohta, who studied regional veins in surgically removed carcinoma of the stomach. He was able to demonstrate, even in vessels that did not have obvious thrombi, by careful techniques such as those described by O'Neill and Samuels, that many "microthrombi" were present. In some cases the microthrombi consisted merely of small platelet aggregates. It is easy to see that if such lesions are present in patients with a primary underlying disease, one or

more of them can become the site of a clinically evident thrombus.

PROBLEMS OF NATURAL RESISTANCE

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Abstract is not available; discussion of the paper is therefore omitted.

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