

Delayed Blood Coagulation in Rabbits with Localized Shwartzman Reaction. (22115)

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In previous work(1) the authors elaborated a procedure indicating the presence or absence of fibrinogen in serum derived from minimally heparinized blood. Subsequently, a correlation between the utilization of fibrinogen and the rheumatic state was attempted. The results seemed to indicate an accelerated fibrinogen polymerization in active rheumatic disease. In order to obtain experimental verification of the reported clinical findings this procedure, described as "fibrinogen polymerization test"(2), was applied to rabbits in which a Shwartzman phenomenon had been produced. Minimally heparinized rabbit blood withdrawn 24 hours after the provocative intravenous injection of endotoxin failed, however, to coagulate within an observation period of 7 or 8 hours so that the test could not be carried out properly, since gross coagulation of the heparinized specimen is a prerequisite. This observation seemed to indicate delayed coagulation independent of the *in vitro* addition of minimal amounts of heparin. Consequently, it was postulated that the Shwartzman phenomenon may be associated with a prolonged Lee-White clotting time. Verification of this assumption was sought in the experiments reported herein.

Materials and methods. Twenty rabbits of either sex, each weighing approximately 2 kg, received 0.5 cc of meningococcus endotoxin* intradermally, followed by the intravenous administration of 2.0 cc of endotoxin 24 hours later. On the 3rd, 4th, 5th and 8th day of the experiment, Lee-White clotting times were determined with blood withdrawn by cardiac puncture. About 15 cc were swiftly aspirated after careful shaving of the precordium and palpating of the point of maximum car-

diac impulse. Only a portion of the aspirated 15 cc were utilized for the Lee-White clotting time, thus leaving a considerable amount of blood within the syringe assumed to contain most of the tissue juice with its thromboplastic properties. Three glass tubes measuring 14 mm x 10 cm were utilized for the determination of the Lee-White clotting time. About 2 cc of blood were placed into each tube. A fourth, graduated centrifuge tube containing 0.2 cc of 0.1 molar solution of sodium citrate was filled up to the 2 cc mark and served for the determination of prothrombin time according to the photo-electric modification of the one-stage Quick method(3). Lee-White clotting times were obtained at room temperature which varied from 22°-26°. The end point at which the clotting time was read coincided with the formation of a solid clot which permitted the complete inversion of the test tube without displacement of the coagulum.

Results. Typical localized Shwartzman reactions were elicited in 16 of the 20 rabbits employed in this study. Characteristic hemorrhagic necrotic lesions at the site of the sensitizing intradermal injection of the endotoxin appeared well before 24 hours had elapsed after the provocative intravenous administration of the meningococcal endotoxin. As seen from Table I, the mean Lee-White clotting time in all 20 animals was 18 minutes on the third day of the experiment, *i.e.* 24 hours

TABLE I. Mean Lee-White Clotting Times and Prothrombin Times of Rabbit Blood Obtained through Cardiac Puncture at Various Stages of Shwartzman Reaction.

	Days after initiation of experiment			
	3rd	4th	5th	8th
Lee-White clotting time in min.	18	8.3	7.4	4.3
Prothrombin time in sec	6.7	4.5	5.7	7.4

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after the provocative intravenous injection, at which time the Schwartzman reaction was quite pronounced and declined to 8.3, 7.4 and 4.3 minutes on the 4th, 5th and 8th day. No group distinction could be established between the clotting times of the majority of rabbits in which the Schwartzman reaction was visible and the few animals in whom no necrotizing lesion appeared. In a separate group of 10 normal rabbits the clotting time of intracardiac blood was determined at room temperature and found to have a mean value of 5.5 minutes.

Prothrombin times in all animals subjected to the Schwartzman phenomenon appeared to be normal throughout (mean value 6.1 seconds) and did not disclose any definite lengthening, even at the time when the Lee-White clotting times were markedly prolonged.

Discussion. Although no satisfactory explanation of the pathogenesis of the Schwartzman phenomenon has yet been found(4), it is known to be characterized by a hemorrhagic necrosis in the prepared skin site. It seems that the second-provocative-injection of bacterial filtrate leads to injury of the walls of small blood vessels. Moreover, thrombosis of these vessels has been found to be a constant pathological feature(4-6).

The results of our study disclose that the localized Schwartzman reaction is accompanied by a prolongation of the Lee-White clotting time with a mean value of 18 minutes as compared to a normal mean of 5.5 minutes. Although the nature of this prolonged clotting time remains undetermined at present, the release of heparin or heparinoid substances as tissue reaction to anaphylactoid stimuli(7)

seems to offer an explanation. The prolonged clotting time may contribute to the hemorrhagic nature of the Schwartzman reaction. On the other hand, it is not of such magnitude as to prevent the phenomenon as has been achieved with large doses of heparin(8,9), namely 30 mg per kg producing incoagulability of rabbit blood for about 7 hours(6). Nevertheless, it seems to be of interest that rabbit blood which physiologically displays a high degree of hypercoagulability should lose this property when the localized Schwartzman phenomenon is induced. Hypercoagulability of rabbit blood is manifested not only in a relatively short Lee-White clotting time, but also in a rather short prothrombin time (Table I).

Summary. 1. A localized Schwartzman reaction was produced in 20 rabbits. 2. The Lee-White clotting time determined with blood obtained through cardiac puncture was found considerably prolonged when the reaction appeared and gradually returned to normal during the ensuing 6 days.

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