SIMILARITIES IN THE MECHANISMS DETERMINING THE ARTHUS AND SHWARTZMAN PHENOMENA

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PLATE 26

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Arthus was the first to show that the intradermal injection of horse serum in appropriately sensitized rabbits resulted in severe hemorrhagic and necrotic lesions in the skin areas injected (1). Later histopathologic studies have indicated that the characteristically severe and extensive tissue damage occurring during the course of the Arthus phenomenon is due to some form of vascular injury (2, 3), but there is little available information as to the mechanism by which this injury is produced.

The macroscopic and microscopic appearance of the skin lesions of the Arthus phenomenon show certain striking similarities to those of the Shwartzman phenomenon, and the possibility has been considered that similar mechanisms may be operating in both cases (4, 5). The techniques employed for eliciting the two phenomena are ordinarily quite different; the Shwartzman phenomenon is produced by two injections of an appropriate bacterial endotoxin, one given intradermally and the other given intravenously after an interval of several hours, while the Arthus phenomenon is elicited by a single intradermal injection of antigen in a sensitized animal. It has been shown, however, that under appropriate conditions the Shwartzman phenomenon can be elicited by antigen-antibody interaction *in vivo* (5). Black-Shaffer *et al.* (6) have furthermore shown that bacterial products active in eliciting the Shwartzman phenomenon are also capable of greatly intensifying the local tissue damage resulting from repeated intradermal injections of antigen under circumstances leading to the development of the Arthus phenomenon. These demonstrations of the interrelationship between the two phenomena support the concept that the pathogenesis of the skin lesions in both cases may involve certain common factors which have not as yet been clearly defined.

Recent studies on the mechanism of the Shwartzman phenomenon (7–9) have shown: (*a*) that skin areas prepared for this phenomenon exhibit a marked degree of aerobic glycolysis; (*b*) that this alteration in metabolism is largely due to the exudate polymorphonuclear leucocytes which migrate into such

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areas; (*c*) that materials capable of eliciting the Shwartzman phenomenon possess the ability to cause clumping of platelets and leucocytes *in vitro* and *in vivo;* (*d*) that the occurrence of such clumping *in vivo* during the course of the Shwartzman phenomenon is accompanied by a severe leucopenia, due to the accumulation of these aggregates in the capillary beds of internal organs; (*e*) that small blood vessels in prepared skin areas undergo thrombosis or occlusion with masses of leucocytes and platelets; and (*f*) that such cellular thrombosis leads to necrosis of the involved vessels, from which hemorrhage subsequently occurs. In the present communication evidence will be presented to indicate that during the course of the Arthus phenomenon there occur events similar in nature and in sequence to those described above.

Materials and Methods

Animals.—Male and female rabbits, each weighing approximately 2000 gm., were obtained from the Rockefeller Institute stock. Litter mates were used in all experiments.

Antigen.—The antigen used for sensitization was crystalline ovalbumin, prepared from fresh egg whites by the method of Sörensen and Höyrup (10). After three recrystallizations from ammonium sulfate, the material was dialyzed against several changes of distilled water and was then preserved by lyophilization.

Sensitization Procedure.—Each rabbit received a series of intradermal injections of ovalbumin, each injection consisting of 0.2 cc. of a 5 per cent solution of ovalbumin in physiologic saline. Intervals of from 5 to 7 days were allowed to elapse between successive injections, and the sensitization procedure was continued until the local reaction which occurred at the injected skin area consisted of an intense inflammatory response, with a well defined central area of hemorrhagic necrosis, developing within 3 to 4 hours after the intradermal injection. Maximal reactions of this type were obtained in most of the animals after the fifth or sixth injection, during the 4th or 5th week of sensitization, and rabbits exhibiting such reactions will be referred to as "sensitized" animals. Subsequent injections of antigen in "sensitized" animals were followed by reactions of similar intensity, and these will be referred to as "challenging" injections.

Bacterial Endotoxin.—A preparation of meningococcal toxin 44B was generously supplied by Dr. Gregory Shwartzman. A single intradermal injection of 0.2 cc. of a ½ dilution of this material was used to prepare the skin for the Shwartzman phenomenon (5).

Nitrogen Mustard.—"Mechlorethamine hydrochloride," a preparation of methyl-bis(β-chloroethyl)amine hydrochloride, was kindly furnished by Dr. Augustus Gibson of Merck and Co., Inc., Rahway. This material was dissolved in distilled water to give a 1.0 mg./cc. solution immediately prior to injection.

Determination of Aerobic Glycolysis.—Samples of skin weighing approximately 250 mg. were removed from the animals, after sacrifice by a blow on the head. These specimens consisted of full-thickness strips of skin, dissected free of subcutaneous tissue. They were placed in vessels containing 10 cc. of Krebs-Ringer solution, which contained 200 mg. of glucose per 100 cc. and phosphate buffer at pH 7.4. The vessels were gassed with oxygen and then shaken at 37°C. for 1 hour. At the end of this time, 10 cc. of 5 per cent trichloracetic acid was added to each vessel. After filtration, the lactic acid content of the supernatant fluid was determined by the method of Barker and Summerson (11). The skin samples were then dried to constant weight at 105°C., and the lactic acid production of each tissue sample was calculated on the basis of the dry weight, the results being expressed as milligrams of lactic acid produced per gram dry weight of tissue per hour.

Hematologic Determinations.—Blood samples were obtained from the marginal ear veins by allowing freely flowing blood to run into tubes containing an appropriate amount of dried oxalate mixture (12). Total and differential leucocyte counts were performed in the usual manner.

Histologic Preparations.—Samples of skin were removed from the animals as above, and were then placed immediately in neutral formol-saline for fixation. Paraffin embedding was used, and sections were cut at a thickness of 7 μ. The sections were stained with hematoxylin-eosin or with Wright's stain according to the technique of Howell and Donahue (13).

EXPERIMENTAL

Aerobic Glycolysis of Rabbit Skin during the Development of the Arthus Phenomenon.—In these experiments, samples of skin were obtained from sensitized rabbits at various intervals after the intradermal injection of oval-

TABLE I

Aerobic Glycolysis in Rabbit Skin during the Development of the Arthus Phenomenon

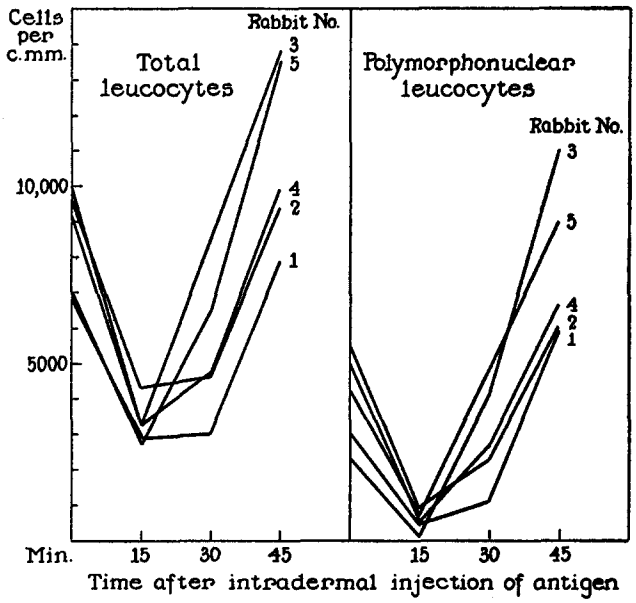
The tissue was incubated for 1 hour in the presence of 200 mg. per cent glucose in Krebs-Ringer solution, with 100 per cent O_2 in the gas phase. The results are expressed as milligrams of lactic acid produced per hour per gram dry weight of tissue.

Rabbit No.	Interval after injection of antigen	Lactic acid production		Increase in aerobic glycolysis
		Injected skin	Normal skin	
	hrs.	*mg./hr.*	*mg./hr.*	*per cent*
1	1	5.37	3.38	59
	2	8.27	3.38	145
2	1	4.78	3.36	42
	2	10.34	3.36	208
3	3	7.12	2.65	170
4	3	8.80	2.18	305

bumin. Samples of normal skin from each animal served as controls. The degree of aerobic glycolysis was determined by the direct chemical measurement of the amount of lactic acid produced during incubation in the presence of oxygen. In some experiments, the aerobic glycolysis of duplicate skin samples was also determined by the manometric method previously described (7). Table I contains representative data obtained from these experiments. It will be seen that a progressive increase in aerobic glycolysis occurred after the injection of antigen. This effect was demonstrable in skin samples removed from the animals 1 hour after the injection, and was considerably more pronounced in samples obtained after intervals of 2 or 3 hours had elapsed. No determinations were attempted on skin samples removed from the animals at intervals longer than 3 hours after the injection of antigen, because of the presence of appreciable hemorrhage and necrosis after that time.

In order to determine whether this phenomenon might be reproduced *in vitro*, samples of skin from sensitized rabbits were incubated for 4 hours in Krebs-Ringer solution containing 0.1 per cent ovalbumin. No detectable increase in aerobic glycolysis occurred under these conditions. This was not an unexpected finding, in view of the observations of Rich (3) and Aronson (14) that tissue from sensitized animals is not demonstrably injured by contact with the specific antigen *in vitro*. The available evidence indicates that the increased aerobic glycolysis described above is probably due to the accumulation in the injected skin areas of "exudate" polymorphonuclear leucocytes, which are known to possess this type of carbohydrate metabolism. The significance of increased aerobic glycolysis as a manifestation of tissue damage has been discussed previously (7), and the possibility that this local metabolic alteration may result in some damage to vascular endothelium has been suggested (9) in the case of the Shwartzman phenomenon.

The Development of Leucopenia During the Arthus Phenomenon.—During the course of this investigation, it was found that a marked leucopenia develops shortly after the intradermal challenging injection of ovalbumin in



TEXT-FIG. 1. The development of leucopenia after the intradermal injection of antigen in sensitized rabbits. The leucopenia can be seen to be due almost entirely to a transitory reduction in the numbers of circulating polymorphonuclear leucocytes. It is similar in degree and duration to the leucopenia known to follow the intravenous injection of glycogen and other materials capable of eliciting the Shwartzman phenomenon.

sensitized rabbits. This effect is mainly due to a profound reduction in the number of circulating granulocytes, as can be seen in Text-fig. 1. The leucopenia is demonstrable within a few minutes after the injection of antigen and is maximal within 15 minutes. In all instances the total numbers of circulating leucocytes had returned to normal or higher than normal values within an hour after the injection had been given. No significant alteration in the total or differential leucocyte count was observed following the intradermal injection of ovalbumin in normal rabbits.

The reason for the transitory disappearance of polymorphonuclear leucocytes from the peripheral circulation after the intradermal injection of antigen is not entirely clear, but possibly it is an expression of a systemic reaction similar to that previously demonstrated in the case of the Shwartzman phenomenon (9). It was shown earlier that the addition of ovalbumin *in vitro* to blood from sensitized rabbits results in a rapid clumping of leucocytes and platelets (9), and Abell and Schenck (15) have demonstrated by the transparent chamber technique that an intravenous injection of antigen is followed by clumping of leucocytes *in vivo* in the rabbit. It has also been shown (16, 17) that the intravenous injection of antigen in sensitized animals results in the development of leucopenia which is similar in degree, in time of onset and in duration to that observed during the present experiments. The leucopenia observed after the intravenous injection of antigen has been shown to be due to the formation of aggregates of leucocytes in the capillary beds of internal organs, especially the lungs, spleen, and liver (18), where they are temporarily segregated from the peripheral circulation. Although no experimental evidence is at hand to indicate whether intradermally injected antigen reaches the general circulation under the conditions of the present experiments, the observed leucopenia may well be due to a mechanism like that described above.

Simultaneous Elicitation of the Arthus Phenomenon and the Shwartzman Phenomenon.—It seemed of interested to investigate further the possibility that the leucopenia described in the preceding section might be a manifestation of some process intimately involved in the mechanism of the Arthus phenomenon. In the case of the Shwartzman phenomenon, it has been shown that the leucopenia which develops after the intravenous challenging injection is the result of a systemic reaction involving the clumping of circulating leucocytes and platelets, and it has further been shown that this process is associated with the development of the local tissue damage in the previously prepared skin areas (10). In order to determine whether a similar reaction occurs following the intradermal injection of antigen in sensitized animals, experiments were designed to determine whether during the course of the development of the Arthus phenomenon hemorrhagic necrosis could be induced in skin areas which had been prepared for the Shwartzman phenomenon.

For this purpose, rabbits sensitized to ovalbumin were prepared for the

Shwartzman phenomenon by the intradermal injection of meningococcal endotoxin in the right upper abdominal quadrant. 24 hours later, each rabbit received an intradermal challenging injection of ovalbumin in an area of the abdomen distant from the area prepared for the Shwartzman phenomenon. Intense hemorrhagic necrotic lesions, typical of the Arthus phenomenon, subsequently developed in all rabbits at the sites of the challenging injection of ovalbumin. In addition, however, similar hemorrhagic and necrotic lesions appeared in the skin areas which had been injected 24 hours earlier with meningococcal endotoxin. In the gross, the reactions at the two sites were indistinguishable. However, it is of some interest that the reactions occurring at the sites of the intradermal injections of meningococcal endotoxin were well developed within 1 hour, while those at the sites of the injections of ovalbumin developed more slowly, over a period of 3 to 4 hours. The significance of this finding will be discussed later.

Leucocyte-Platelet Thrombosis Occurring during the Arthus Phenomenon.—In the experiments now to be described, sensitized animals were sacrificed 1, 2, or 4 hours after the intradermal challenging injection of ovalbumin, and the injected skin areas were removed for subsequent histologic examination. In sections of skin obtained 1 hour after the injection of antigen, the most prominent histologic alteration was a perivascular accumulation of polymorphonuclear leucocytes, involving capillaries and small veins throughout the injected area. Leucocytes could be seen adhering to the walls of these vessels and in various stages of diapedesis. Sections of skin removed 2 hours after the injection of antigen showed an increase in the degree of perivascular leucocytic infiltration, and in addition numerous capillaries and small veins were seen to contain thrombi composed of leucocytes and platelets in various proportions. These thrombi ranged from small parietal aggregations of platelets (Fig. 1) to larger masses of leucocytes and platelets which completely occluded the vessels (Figs. 2 and 3). In the sections of skin removed 4 hours after the injection of antigen, at a time when the Arthus phenomenon was well developed with macroscopic evidence of hemorrhage and necrosis, the leucocyte-platelet thrombosis described above had progressed to involve virtually all of the capillaries and small veins in the injected area, and larger veins, like the one illustrated in Fig. 4, were also found to be occluded. It could be seen that considerable necrosis of many of the thrombosed vessels had occurred. This necrosis involved the leucocytes within and around the vessels, and in many areas destruction of the vessel walls could be observed. Hemorrhage into the tissues had occurred from many of the vessels whose walls had been damaged in this manner. It should be mentioned that not all the capillaries and veins showed the same degree of damage; in individual sections vessels could be found in various stages of involvement, some exhibiting thrombosis without necrotic changes and others showing extensive damage with rupture of the vessel walls and

hemorrhage. In general, it can be said that the changes described above closely resembled the histologic alterations previously described as occurring during the Shwartzman phenomenon (9).

Modification of the Arthus Phenomenon by Nitrogen Mustard.—The inhibition of the Shwartzman phenomenon by nitrogen mustard, originally described by Becker (19), was subsequently shown to be due to the leucopenia produced by

TABLE II

Modification of the Arthus Phenomenon by Treatment of Sensitized Rabbits with Nitrogen Mustard

The five treated rabbits showed no Arthus reactions during the 1st day after the injection of antigen. Four of these rabbits then developed extensive progressing hemorrhagic and necrotic lesions and died at a time when the untreated controls had completely recovered.

	Rabbit No.	Leucocyte counts at time of injection of ovalbumin		Hemorrhagic necrotic skin lesions (hrs. after injection of ovalbumin)					
		Total leucocytes per c.mm.	Granulocytes per c.mm.	4	12	24	48	72	96
Nitrogen mustard treated	1	3600	460	−	−	−	++++	++++*	
	2	3400	525	−	−	−	+	−	
	3	400	0	−	−	+	++++	++++	++++*
	4	550	33	−	−	+	++++	++++*	
	5	2700	350	−	−	−	++++	++++*	
Controls	6	7750	2580	++++	++++	+++	+	−	
	7	8500	2800	++++	+++	+	−	−	
	8	7900	2840	++++	++++	++	+	−	
	9	8900	2750	++++	++++	++	±	−	
	10	7950	2160	++++	+++	+	−	−	

− indicates the absence of hemorrhage or necrosis at the site of the injection of ovalbumin.

+ to ++++ indicates roughly the size and severity of the lesions developing at the site of the injection of ovalbumin.

* Dead.

this agent (8). It appears that in the absence of circulating polymorphonuclear leucocytes, adequate preparation of the skin for the Shwartzman phenomenon cannot be accomplished. Dammin and Bukantz (20) reported that the Arthus phenomenon could be inhibited by treatment of rabbits with nitrogen mustard during the period of sensitization, and they attributed this effect to a depression of antibody formation. Because of the apparent close relationship between the mechanisms involved in the Shwartzman phenomenon and the Arthus phenomenon, it was of interest to determine whether the Arthus phenomenon

could be inhibited or suppressed by a single injection of nitrogen mustard in fully sensitized rabbits.

For this experiment, ten sensitized rabbits were used. Nitrogen mustard was given intravenously to five of these animals, each receiving a single dose amounting to 1.9 mg./kilo, and total and differential leucocyte counts were performed at daily intervals thereafter. Within 4 days, all the treated rabbits had developed severe leucopenia and granulocytopenia as will be seen in Table II, and at this time all ten rabbits were given challenging intradermal injections of ovalbumin. Although no measurements of circulating antibody levels were made before or after the treatment with nitrogen mustard, the relatively short time required for this experiment makes it seem likely that any alterations in the antibody level produced by nitrogen mustard would be minimal (21).

The five control rabbits developed local hemorrhagic necrotic lesions typical of the Arthus phenomenon, which were maximal within 5 hours after the injection of antigen and gradually subsided during the next 2 days. In contrast, the five animals which had received nitrogen mustard showed no evidence of local inflammatory reaction at the site of the injection of ovalbumin for 24 hours. During the 2nd and 3rd days after the injection of antigen, however, small nodular lesions developed at the site of the injection of antigen in four of these animals, and these lesions rapidly became hemorrhagic and necrotic and progressed to involve large areas of the abdominal wall. Within 4 days after the injection of the antigen, these four animals had succumbed, and at time of death the lesions of the abdominal wall were more severe and several fold larger than those in any of the typical Arthus phenomena observed during the course of this study. The cause of death in these animals is not known. Hematologic studies were not carried out after the 1st day following the injection of antigen, and pathologic examinations were not performed. It would appear that prior treatment of sensitized animals with nitrogen mustard interferes with the normal response to local antigen-antibody interactions, and that the typical Arthus phenomenon does occur not under these circumstances. The consequences of such interference appear to be drastic, and it is planned to investigate further the problem they present.

DISCUSSION

The experimental evidence just set forth shows that the intradermal injection of antigen in a sensitized animal is followed by (*a*) the perivascular accumulation of polymorphonuclear leucocytes in the injected area, with a consequent local alteration in metabolism, and (*b*) a systemic reaction, involving the intravascular aggregation of platelets and leucocytes, which results in cellular thrombosis of the capillaries and veins in the injected skin areas. The necrosis and hemorrhage which follow would appear to be due to the disturbance of local blood supply.

The similarity between this interpretation of the Arthus phenomenon and that previously advanced in connection with the Shwartzman phenomenon (9) is readily apparent. In Table III a comparison of the results of various metabolic, hematologic, and histologic studies of both phenomena is presented, and it will be seen that a close correspondence exists between them with respect to each of the aspects considered. The skin lesions of both the Arthus and the Shwartzman phenomena are associated with a peculiar form of vascular injury, manifested in each case by leucocyte-platelet thrombosis. The evidence supports the concept that closely similar mechanisms are operating in the production of this vascular injury in both cases.

TABLE III

Comparison of Hematologic, Metabolic, and Histologic Studies of the Arthus Phenomenon and the Shwartzman Phenomenon

Aspect studied	Occurrence in	
	Arthus phenomenon	Shwartzman phenomenon
(*a*) Perivascular accumulation of polymorphonuclear leucocytes in injected skin area.	+	+
(*b*) Development of increased aerobic glycolysis in injected skin area.	+	+
(*c*) Production of leucocyte-platelet clumping *in vitro* by agent used for eliciting the phenomenon.	+	+
(*d*) Development of leucopenia following injection of agent used for eliciting the phenomenon.	+	+
(*e*) Occurrence of leucocyte-platelet thrombosis of capillaries and small veins in injected area.	+	+
(*f*) Subsequent development of hemorrhage from vessels involved in cellular thrombosis.	+	+

For purposes of discussion, the Arthus and the Shwartzman phenomena can both be considered to be the result of two distinct processes: (*a*) the development of certain local environmental conditions which render the blood vessels in the area vulnerable to cellular thrombosis, and (*b*) the occurrence of a systemic reaction, involving alterations in leucocytes and platelets. In the case of the Shwartzman phenomenon, this distinction is perceptible in what happens after the two injections required to produce the hemorrhagic necrotic lesion. The preparatory intradermal injection results in the establishment of the necessary local conditions and vascular susceptibility, while the challenging intravenous injection induces a systemic leucocyte-platelet clumping with subsequent thrombosis of the vessels in the prepared skin area (9). In the case of the Arthus phenomenon, a single injection suffices for the development of the local lesion, and the two processes outlined above may be considered as taking place concurrently. The injection of antigen is followed by a

local accumulation of leucocytes and the development of vascular susceptibility, and at the same time a systemic reaction occurs which results in leucocyte-platelet thrombosis of the vulnerable capillaries and veins in the injected skin area. This interpretation is in accord with the results of the experiment in which the Shwartzman phenomenon and the Arthus phenomenon were simultaneously elicited, the lesions of the Arthus phenomenon requiring a considerably longer time for their appearance, presumably because of the time required for the local environmental alterations to occur.

It is true that this hypothesis on the nature of the vascular damage occurring during the Arthus phenomenon is largely based on morphologic data, and leaves unanswered many of the fundamental questions relating to the mechanism of the observed processes. The nature of the chemotaxis produced by *in vivo* antigen-antibody interactions (2) and the significance of the high degree of aerobic glycolysis exhibited by "exudate" leucocytes are matters for further investigation. It has been suggested that the vulnerability of blood vessels in certain tissues to leucocyte-platelet thrombosis is related to the presence in such tissues of an active aerobic glycolysis (9), but it is by no means clear whether this is because of a direct effect of lactic acid on vascular endothelium, or is due to other, more complex, local environmental factors. No satisfactory explanation can as yet be offered for the mechanism by which ovalbumin produces clumping of leucocytes and platelets in the blood of sensitized rabbits. Recent advances by Lutz (22) have stimulated interest in the general phenomena of intravascular agglutination of leucocytes and platelets, and it is possible that newer techniques may provide a better understanding of this process. It is possible that local accumulation of lactic acid results in death and autolysis of the leucocytes in the cellular thrombi and in the perivascular exudate (9), and that the cathepsins released from these cells play a role in the subsequent disruption of the vessel walls (7). In sum, the factors involved in the ultimate necrosis of the thrombosed blood vessels and the production of hemorrhage from these damaged vessels require further study.

The demonstration of the basic similarity between the vascular injury of the Shwartzman phenomenon and that of the Arthus phenomenon may be of considerable significance. The fact that a wide variety of antigens are capable of producing the Arthus phenomenon, when taken with the finding that numerous bacteria and bacterial products are active in eliciting the Shwartzman phenomenon suggests that the tissue reaction occurring may be of importance in the pathogenesis of certain infectious diseases and in the development of various phenomena associated with the "immune" or "hypersensitive" state.

SUMMARY

The intradermal injection of ovalbumin in rabbits sensitized to this antigen, under circumstances resulting in the elicitation of the Arthus phenomenon,

causes a systemic reaction involving alterations in leucocytes and platelets, and results in cellular thrombosis of capillaries and veins in the injected skin areas. An abnormal metabolic process develops in the injected skin areas and may be the cause of the vulnerability of these vessels to leucocyte-platelet thrombosis. The form of vascular damage determining the Arthus phenomenon is similar to that already observed in the case of the Shwartzman phenomenon, and the results of various metabolic, hematologic, and histologic studies indicate that the mechanisms resulting in both phenomena are closely related.

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EXPLANATION OF PLATE 26

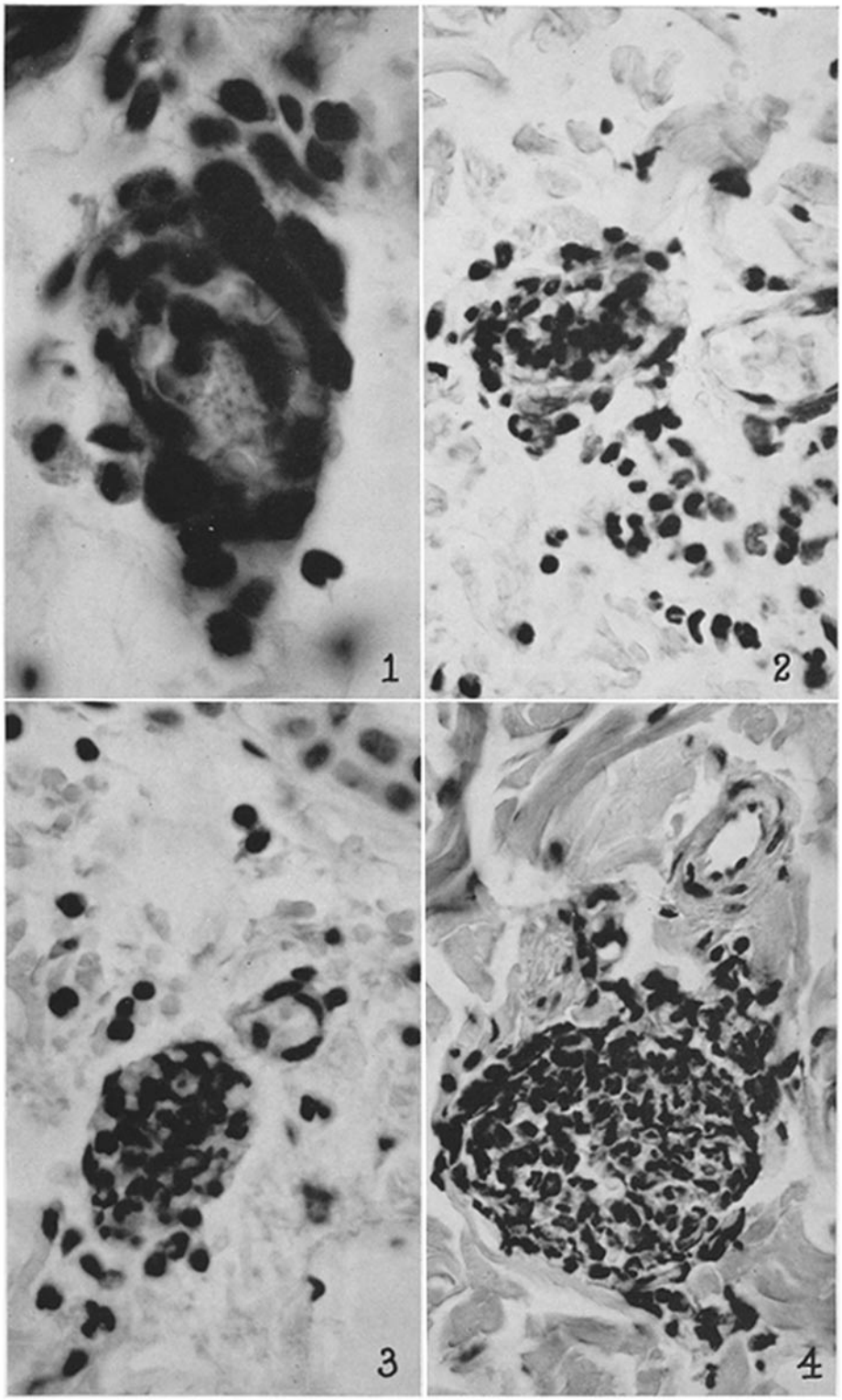
The photomicrographs were made by Mr. Richard F. Carter.

Figs. 1 to 4 are photomicrographs of material provided by an experiment described in the text (p. 352). The sections were stained with Wright's stain.

FIG. 1. A small vein in the skin of a sensitized rabbit 1 hour after the intradermal injection of antigen. The perivascular leucocytic accumulation and the partial occlusion by a parietal platelet thrombus are characteristic features of the appearance of such small vessels at this early stage of the Arthus phenomenon. × 590.

FIGS. 2 AND 3. The appearance of small veins in the skin of sensitized rabbits 2 hours after the injection of antigen. These vessels are occluded by thrombi which consist in the main of polymorphonuclear leucocytes. × 345.

FIG. 4. A larger vein in the skin of a rabbit sacrificed 4 hours after the intradermal injection of antigen, showing a thrombus composed mainly of leucocytes, with numerous platelets interspersed among these cells. The similarity of this leucocyte-platelet thrombosis to that found in the Shwartzman phenomenon is discussed in the text. × 236.



(Stetson: Arthus and Shwartzman phenomena)