

## THE OCCURRENCE OF LEUCOCYTE-PLATELET THROMBOSIS IN RHEUMATIC CARDITIS

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PLATES 27 AND 28

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Studies have recently been carried out in this laboratory on the mechanism of tissue damage by bacterial endotoxins and by antigen-antibody interactions *in vivo*. The Arthus and Shwartzman phenomena have been used as laboratory models in these studies, and it has been found that the characteristic hemorrhagic and necrotic cutaneous lesions which occur during the course of both of these phenomena are the result of thrombosis or occlusion of capillaries and small veins with masses of leucocytes and platelets (1, 2). Interruption of blood supply by the thrombi leads to necrosis of the involved vessels, followed by hemorrhage and destruction of the surrounding tissues. The factors contributing to the development of these leucocyte-platelet thrombi include (a) an alteration in leucocytes and platelets, resulting in a tendency toward intravascular aggregation of these elements, and (b) a local alteration in the endothelium of small blood vessels, possibly related to the development of an abnormal form of carbohydrate metabolism in the tissues about these vessels (2).

It has been suggested that a mechanism like that described above may be operating in the pathogenesis of certain human diseases (2), and the present study was undertaken as a preliminary attempt to explore this possibility. Pathologic material derived from patients succumbing during the course of rheumatic fever and other acute and chronic diseases has been examined for the presence of leucocyte-platelet thrombi, and this form of vascular damage has been found to be regularly present in association with other histopathologic manifestations of active rheumatic carditis. In the present communication, the results of this examination are presented with a discussion of certain considerations bearing on the significance of the observations.

### *Materials and Methods*

The pathologic material described in this report consisted of cardiac tissue which had been fixed either in formalin or in Zenker's fluid. The microscopic sections had been stained with

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TABLE I

*The Occurrence of Leucocyte-Platelet Thrombi in the Hearts of Patients Succumbing during the Course of Active Rheumatic Fever*

Case No.	Classification	Age at death	Year of death	Duration of disease	Leucocyte-platelet thrombosis	Aschoff bodies
<b>Group I</b>						
1	Early active rheumatic carditis	16	1924	14 days	+	+
2		19	1929	98 "	+	+
3		12	1933	42 "	+	+
4		16	1937	60 "	+	+
5		12	1951	18 "	+	+
6		12	1939	14 "	+	+
<b>Group II</b>						
7	Chronic rheumatic carditis	13	1936	3 mos.	-	-
8		51	1941	2 yrs.	-	-
9		10	1934	1 yr.	-	-
10		7	1933	4 mos.	+	+
11		9	1922	1 yr.	-	-
12		10	1923	4 mos.	+	+
<b>Group III</b>						
13	Rheumatic heart disease without evidence of active carditis	17	1929		-	-
14		46	1930		-	-
15		26	1932		-	-
16		60	1932		-	-
17		28	1933		-	-
18		17	1934		-	-
19		38	1936		-	-
20		61	1936		-	-
21		55	1936		-	-
22		20	1937		-	-
23		11	1938		-	-
24		29	1938		-	-
25		45	1938		-	-
26		44	1940		-	-
27	43	1941		-	-	
<b>Group IV</b>						
28	Subacute bacterial endocarditis, rheumatic heart disease	16	1931	6 mos.	+	+
29		23	1938	7 "	+	+
30		51	1940	?	-	-

\* The thrombi observed in this case were composed exclusively of platelets. The patient exhibited a severe granulocytopenia during the last 2 weeks of life, following a prolonged course of pyrimidon therapy.

TABLE I—*Concluded*

Case No.	Classification	Age at death	Year of death	Duration of disease	Leucocyte-platelet thrombosis	Aschoff bodies
Group V						
31	Luetic aortitis, aneurysm	48	1923	6 mos.	—	—
32	Hypertensive heart disease	71	1924	3 yrs.	—	—
33	Lobar pneumonia	23	1924	4 days	—	—
34	Hemolytic streptococcal septice- mia	51	1925	5 “	—	—
35	Tuberculous meningitis	17	1929	5 mos.	—	—
36	Pulmonary tuberculosis	46	1929	3 yrs.	—	—
37	Agranulocytic angina	54	1933	14 days	—	—
38	Lobar pneumonia	58	1933	4 “	—	—
39	Chronic glomerulonephritis	16	1934	6 yrs.	—	—
40	Lobar pneumonia	34	1936	4 days	—	—
41	Myelogenous leucemia	69	1938	9 mos.	—	—
42	Lobar pneumonia	56	1938	9 days	—	—
43	Coronary occlusion	42	1938	12 “	—	—
44	Periarteritis nodosa	35	1938	2 yrs.	—	—
45	Acute bacterial endocarditis	31	1939	6 days	—	—
46	Thrombophlebitis	46	1940	4 “	—	—

hematoxylin-eosin or with eosin-methylene blue. In some cases, the original blocks of tissue were available and new sections were cut and stained with Wright's stain (3), which has been found to provide better differentiation of the elements of leucocyte-platelet thrombi.

The cases studied included those of all patients succumbing in this hospital since 1922 in which there was gross or microscopic evidence of rheumatic heart disease. The hospital records of these patients were examined for clinical and laboratory evidence of the presence of rheumatic activity during the year preceding death. This evidence was evaluated in terms of the criteria suggested by Jones (4). In those cases in which active rheumatic fever was judged to have been present, the duration of the disease process was determined as the interval from the onset of the first manifestation of rheumatic activity to the time of death. The study also included material from patients succumbing in this hospital to diseases other than rheumatic fever and rheumatic heart disease. Examination of the hospital records of these patients failed to reveal any evidence of rheumatic fever, and whenever possible the duration of the disease responsible for death was determined as above. The data obtained in this manner were used in the following classification of the cases studied.

*Group I.*—This group consisted of six patients who succumbed during attacks of rheumatic fever and who exhibited definite evidence of rheumatic activity during the 2 weeks prior to death.<sup>1</sup>

*Group II.*—Included in this group were six patients in whom the rheumatic process was judged to have been inactive during the 2 weeks before death. In none of these cases were any of the major manifestations of rheumatic fever (4) present during this period, although

<sup>1</sup> The author is indebted to Dr. May Wilson for permission to include in this group a patient (Case 6, Table I) on whom autopsy was performed at the New York Hospital.

in each case there had been unequivocal evidence of rheumatic activity during the year prior to death.

*Group III.*—This group was composed of fifteen patients suffering from rheumatic heart disease resulting from previous attacks of rheumatic fever. In no case was there evidence of active rheumatic fever during the last year of life.

*Group IV.*—This group included three patients in whom the terminal illness was subacute bacterial endocarditis superimposed on rheumatic heart disease of several years' standing. The infecting organism in each case was an  $\alpha$ -hemolytic streptococcus. Because of the difficulty in determining the presence or absence of coexisting rheumatic activity in these patients, they were placed in a group separate from the other rheumatic patients.

*Group V.*—None of the patients in this group had a history of rheumatic fever, and all succumbed to some acute or chronic illness other than rheumatic fever or rheumatic heart disease.

Histopathologic examination of cardiac tissue from these patients was carried out with the aim of establishing the presence or absence of rheumatic carditis. The sole diagnostic criterion used was the presence or absence of the typical Aschoff body as described by Gross and Ehrlich (5). In each case a search was also made for leucocyte-platelet thrombi of the type already described (1, 2).

#### RESULTS

The leucocyte-platelet thrombi observed during the course of this study were similar in general appearance to those already shown to be involved in the pathogenesis of the Schwartzman and Arthus phenomena in the rabbit. They consisted of masses of platelets and leucocytes which more or less completely filled the lumina of the involved vessels. The proportion of leucocytes to platelets was variable, and portions of some thrombi apparently consisted exclusively of one or the other of these components. The appearance of thrombi typical of those observed in this study is illustrated in Figs. 1 to 8.

The vessels most commonly found to be involved were small veins (Figs. 1 to 3, 5, and 6) and capillaries (Figs. 4 and 7), although thrombi were also observed in occasional arterioles (Fig. 8). Leucocyte-platelet thrombi were not found in larger branches of the coronary arteries and veins. The thrombi were observed most frequently in the vessels of the myocardium and pericardium, but were also seen in the subendocardium, in the adventitia of the aorta, and occasionally in valves. Figs. 1 to 4 illustrate the appearance of vessels in the pericardium of one of the patients with active rheumatic carditis (Case 5, Table I). In Fig. 7 may be seen the appearance of myocardial capillaries containing similar cellular thrombi (Case 2, Table I), while Figs. 5 and 6 illustrate leucocyte-platelet thrombosis of larger veins in the myocardium (Case 6, Table I).

In Table I can be seen the correlation between the occurrence of these vascular lesions and the clinical and pathologic evidence of active rheumatic fever. In Group I, consisting of patients in whom the rheumatic process was of relatively short duration and of relatively severe degree at the time of death, leucocyte-platelet thrombosis was prominent in every case. In Group II, com-

posed of patients with rheumatic fever of longer duration and of a low degree of activity during the period of 2 weeks prior to death, leucocyte-platelet thrombosis was found in only two cases, and these were the only cases in this group which showed other histologic evidence of active rheumatic carditis. No leucocyte-platelet thrombi were found in the hearts of patients in Groups III and V, consisting respectively of patients with rheumatic heart disease but with no evidence of rheumatic fever during the year preceding death and patients with acute or chronic diseases other than rheumatic fever. In Group IV, consisting of three patients succumbing to subacute bacterial endocarditis superimposed on rheumatic heart disease, one patient (Case 30) showed no leucocyte-platelet thrombi and no histopathologic changes characteristic of active rheumatic carditis. The other two patients (Cases 28 and 29), 16 and 23 years of age respectively, showed definite Aschoff bodies and in both of these cases leucocyte-platelet thrombi were observed.

In none of the cases in which leucocyte-platelet thrombi were found was there a consistent correlation between the location of these thrombi and the location of Aschoff bodies. In general it can be stated that the thrombi were more frequently encountered in areas of myocardium in which Aschoff bodies were most numerous and less frequently found in relatively normal portions of the myocardium. In the pericardium, leucocyte-platelet thrombi were consistently found in those areas showing evidence of fresh pericarditis, and frequently the thrombi appeared to be associated with small focal hemorrhages.

#### DISCUSSION

The results of this study indicate that leucocyte-platelet thrombosis of capillaries and small veins is a prominent feature of active rheumatic carditis. A consistent correlation was found between the occurrence of these vascular lesions and the presence of Aschoff bodies in the hearts of patients dying during the course of rheumatic fever. The significance of this finding is not clear. While it is possible that this form of vascular damage may be involved in the subsequent development of other more generally recognized manifestations of tissue damage during the course of rheumatic carditis, the limitations of the data and material available during this study do not permit such a conclusion. It is hoped that future examination of pathologic material derived from patients earlier in the course of rheumatic fever will result in a better understanding of the sequence of events involved, and permit an evaluation of the significance of this vascular lesion.

Leucocyte-platelet thrombosis has apparently not previously been described in association with active rheumatic carditis. In a survey of the vascular lesions occurring during rheumatic fever, von Glahn and Pappenheimer (6, 7) do not report the phenomenon, and Sachs (8), in an extensive review of the

histopathologic features of rheumatic carditis, does not mention these vascular lesions. However, Gross, Kugel, and Epstein (9) studied lesions of the coronary blood vessels occurring during acute rheumatic fever and report the occasional finding of "granular plugged vessels." They ascribed this lesion to a proliferation of the endothelium of small branches of the coronary arteries, with subsequent granular transformation of the protoplasm. The appearance of the lesion in the photomicrograph which accompanies their report is quite similar to that of the vessel in Fig. 8. Although a complete review of the voluminous literature on the pathogenesis of rheumatic fever has not been attempted, no further observations bearing on the leucocyte-platelet thrombosis observed during this study have been found. It may be pertinent to note, however, that rheumatic verrucae have been shown to consist of masses of blood platelets with enmeshed leucocytes, erythrocytes, and strands of fibrin (8). These verrucae, usually located along the lines of closure of valves, might thus be considered to be parietal thrombi, and it is possible that common factors may be involved in the production of such deposits and in the formation of the leucocyte-platelet thrombi observed in the smaller coronary vessels.

The mechanism whereby leucocyte-platelet thrombosis is brought about during the course of rheumatic carditis is not clear. The possibility has been considered that this phenomenon may result from some agonal or postmortem process. Such an interpretation seems unlikely in view of the observations that these thrombi are not found in the larger branches of the coronary arteries and veins and are not found in the hearts of patients in the absence of acceptable evidence of active rheumatic carditis. In view of the fact that leucocyte-platelet thrombi have been shown to be associated with the development of extensive tissue damage during the course of the Arthus and Shwartzman phenomena, the concept that the thrombi described above are of significance in the pathogenesis of rheumatic carditis may form a useful working hypothesis for further investigation.

#### SUMMARY

Leucocyte-platelet thrombi, involving the smaller branches of the coronary blood vessels, have been found in the hearts of patients with active rheumatic fever and rheumatic carditis. A consistent correlation has been observed between the existence of these vascular lesions and the presence of typical Aschoff bodies. It is suggested that these cellular thrombi may play a role in the pathogenesis of rheumatic carditis.

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## EXPLANATION OF PLATES

The photomicrographs were prepared by Mr. Richard Carter.

Figs. 1 to 8 are photomicrographs of material described in the text (Table I).

## PLATE 27

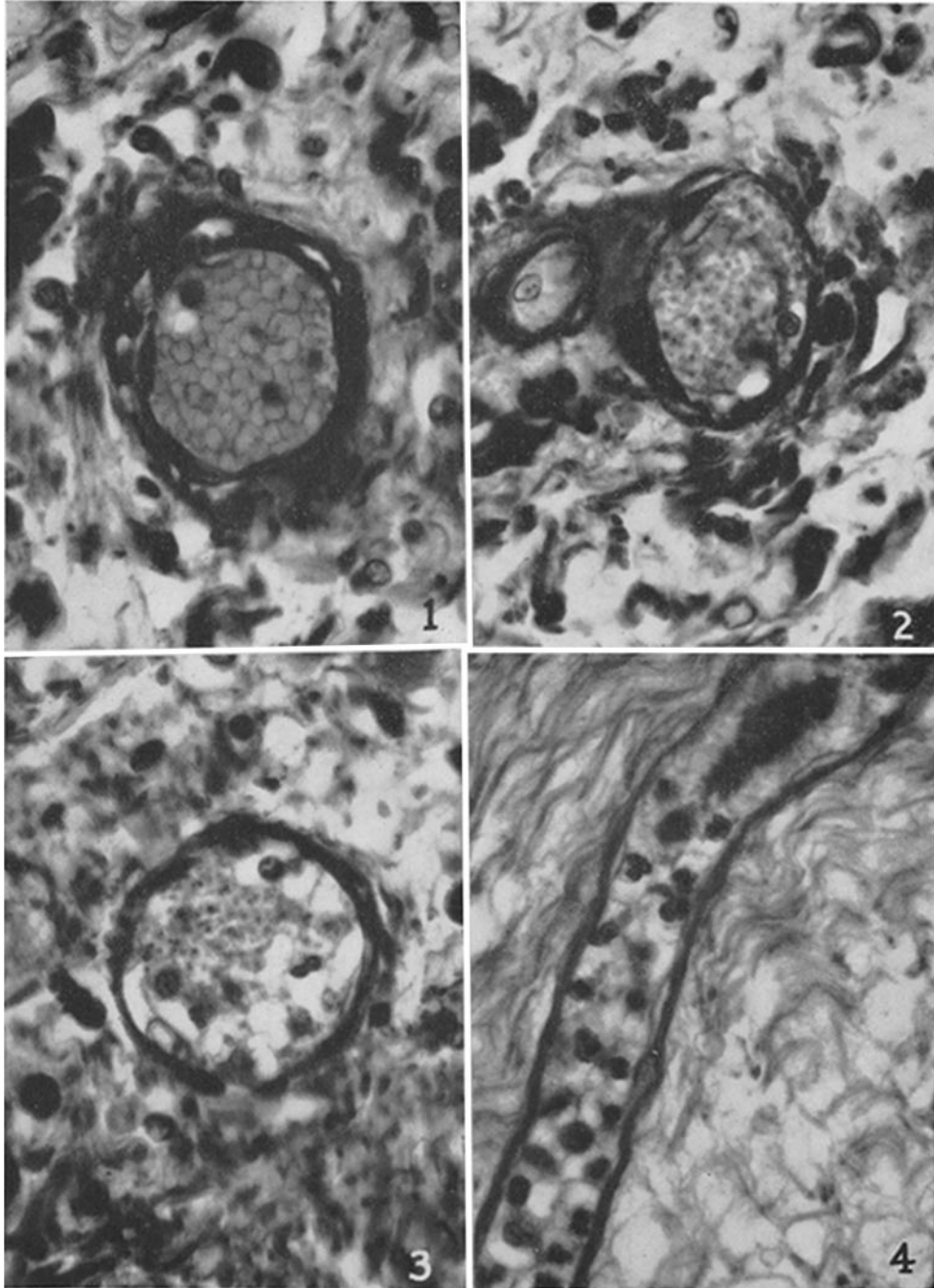
FIG. 1. Pericardium, Case 5. A small vein, with the lumen filled with erythrocytes and no evidence of leucocyte-platelet thrombosis. Wright's stain.  $\times 743$ .

FIG. 2. Pericardium, Case 5. A small vein with a mass of platelets occupying the lumen. Wright's stain.  $\times 743$ .

FIG. 3. Pericardium, Case 5. Another small vein containing a thrombus composed in part of platelets and in part of leucocytes. Wright's stain.  $\times 743$ .

FIG. 4. Pericardium, Case 5. A capillary containing leucocytes and, in the upper portion, a mass of platelets. Wright's stain.  $\times 743$ .





(Stetson: Leucocyte-platelet thrombosis in rheumatic carditis)

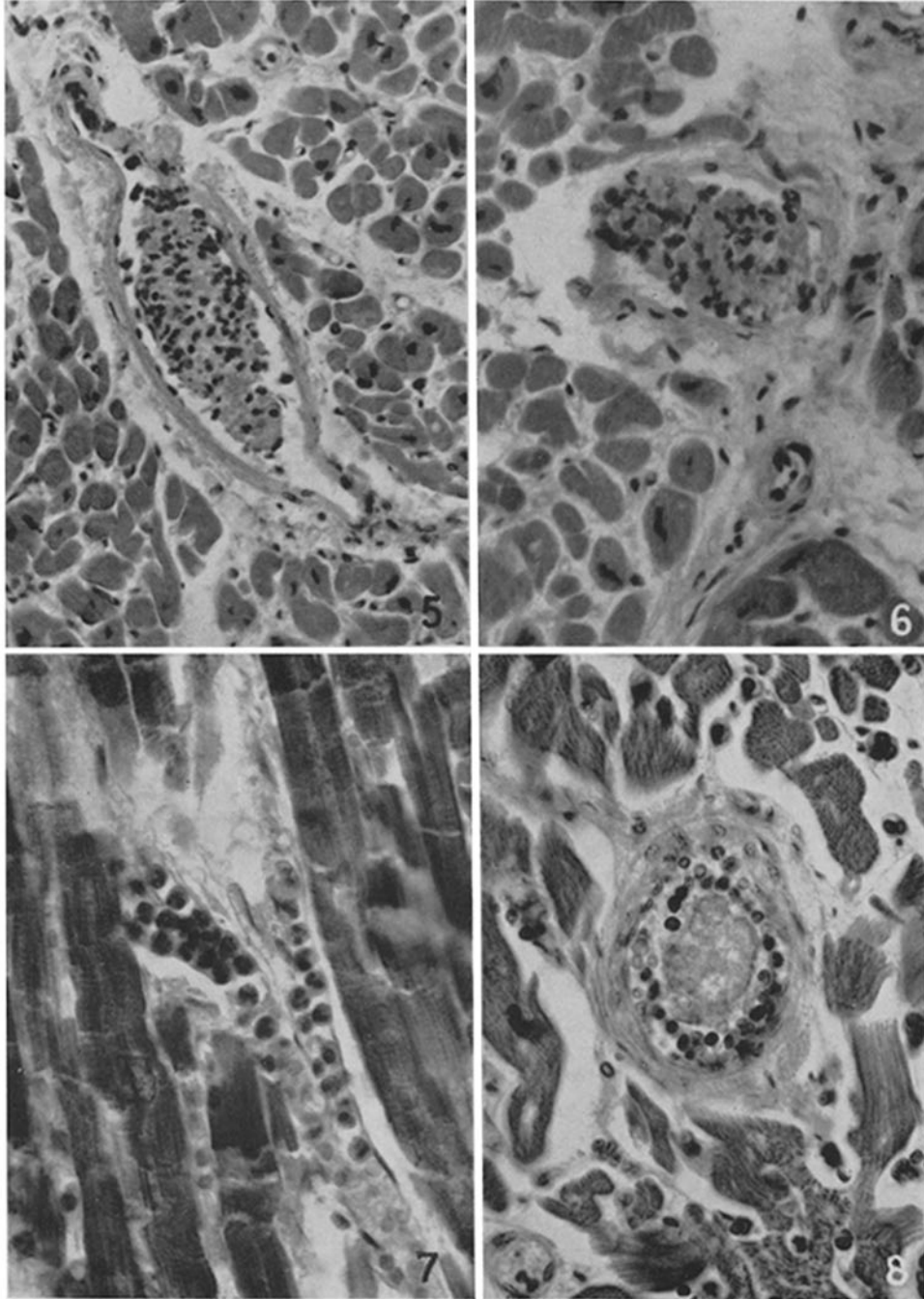
PLATE 28

FIG. 5. Myocardium, Case 6. A thrombus occupies the lumen of the vein. Higher magnification revealed the thrombus to be composed of platelets with numerous enmeshed leucocytes. Hematoxylin-eosin.  $\times 276$ .

FIG. 6. Myocardium, Case 6. A similar thrombus occupying the lumen of another vein. Hematoxylin-eosin.  $\times 382$ .

FIG. 7. Myocardium, Case 4. A branching capillary with leucocytes filling the lumina of both branches. Wright's stain.  $\times 525$ .

FIG. 8. Myocardium, Case 2. A small artery containing a thrombus composed mainly of platelets. The thrombus is not adherent to the endothelium, and the intervening space is occupied by erythrocytes and a few leucocytes. Eosin-methylene blue.  $\times 430$ .



(Stetson: Leucocyte-platelet thrombosis in rheumatic carditis)