STUDIES ON THE COAGULATION DEFECT IN A CASE OF THROMBOCYTOPENIC PURPURA COMPLICATED BY THROMBOSIS *

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Recent investigations have demonstrated that thrombosis can be prevented by the administration of anticoagulant drugs.[1] It is therefore of interest to observe a case in which thrombosis occurred in the course of a hemorrhagic syndrome featured by marked prolongation of the coagulation time of the blood. We wish to report such a case, with experimental observations on the nature of the coagulation defect, and to give a brief review of the literature dealing with the coagulation time in thrombocytopenic purpura and the neurologic complications of that condition.

The Coagulation Time in Thrombocytopenic Purpura

Although the blood platelets yield the principal source of thromboplastin for the coagulation of shed blood, there is no significant correlation between the coagulation time and the platelet count. In a group of 139 paired determinations of these factors on the venous blood in experimental thrombocytopenic purpura in dogs, Tocantins [2] found an insignificant correlation of minus 0.234 ± 0.069. In our group of 743 observations of 402 patients suffering from various diseases, the coefficient of association (Yule's Q) between the same two factors was 0.20 ± 0.16, showing no association in the group tested.[3]

In the great majority of cases reported in the literature, the coagulation time in thrombocytopenic purpura appears to have been within the normal range for the methods employed (usually under 10 minutes). However, Evans [4] found a slight prolongation of the coagulation time which returned to normal coincident with elevation of the platelet count in 8 patients who were splenectomized. Other cases in which the coagulation time was slightly or moderately prolonged (up to 25 minutes) have been observed.[4,6,7,8] Tidy [5] stated that 'At present the fact is established that coagulation time is slightly, but not greatly, increased in haemorrhagic purpura. The reason for this is still uncertain."

In thrombocytopenic purpura a slight or moderate prolongation of the coagulation time is not unusual, but a *marked* prolongation has seldom been observed. Marzollo's [9] case was that of a 3-year-old girl. The platelets numbered between 10,000 and 80,000 per cmm., and the

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coagulation time, tested by various methods, was 23 to 160 minutes. As clinical improvement took place, the platelet count rose to 120,000 per cmm., and the coagulation time returned to normal.

The case reported by Aubertin and Lafon [10] was that of a man, 19 years of age. Examination 1 month before death showed a markedly prolonged bleeding time and a nonretractile blood clot. The platelets numbered 136,000 per cmm. and the coagulation time was 10 minutes. Five days before death the platelets numbered 182,000 per cmm. and the coagulation time was greater than 2 hours. On the day before death the coagulation time was markedly prolonged; after standing overnight at room temperature, coagulation had taken place only in that part of the specimen occupied by the sedimented erythrocytes; the supernatant plasma remained completely liquid.

Neurologic Complications of Thrombocytopenic Purpura

Intracerebral hemorrhage has been the most frequently reported neurologic complication of thrombocytopenic purpura.[11-21] In some patients the hemorrhages have been large and solitary; in some, small and multiple; and in others they have ruptured into the subdural space or into the ventricles. In addition there have been many reports of primary subdural or subarachnoid hemorrhage.[10,18-24] Unlike hemophilia, a number of cases of cerebellar hemorrhage have been encountered in thrombocytopenic purpura.[18,20] Less commonly, hemorrhages have occurred in the midbrain,[18,25] the pituitary gland,[26] the optic tracts,[25,27] the spinal cord,[28,29] and the spinal meninges.[18] No reports of peripheral nerve involvement in thrombocytopenic purpura have come to our attention. This is in contrast to hemophilia, in which such lesions are rather frequently encountered.[30] We have found no reports indicating a disturbance in the cranial venous sinuses in thrombocytopenic purpura except in the case reported by Welt and Kasnetz [33] in which thrombocytopenic purpura occurred as a complication of acute mastoiditis with lateral sinus thrombosis, *Streptococcus viridans* bacteremia, and multiple metastatic abscesses.

Report of Case *

W. J. F. (no. U 79071) was a white male machine operator, 29 years of age, who entered the University of California Hospital on December 4, 1941.

History. The family history was irrelevant for bleeding diseases. No cause of secondary thrombocytopenic purpura was discovered in the past history. At the age of 19 years the patient had suffered from toxic hepatitis following the administration of neoarsphenamine given for an indolent ulcer of the left lower leg. The ulcer persisted, and in 1939 and 1940 additional ulcerated areas appeared on the dorsal surfaces of both feet. In recent months the lesions had healed, leaving

* A brief summary of this case has been published previously.[49]

heavily pigmented scars. He had had a nonproductive cough for many years and for the past 3 years had suffered from dyspnea on exertion, ankle edema, and nocturia. For the past 6 months he had experienced increasing "stiffness" of the leg muscles. The patient had bruised easily since childhood. During the past year bouts of epistaxis had occurred with increasing frequency and severity and numerous petechial hemorrhages had appeared in successive showers over the lower extremities. He had also noted bright red blood in the stool on numerous occasions.

Physical Examination. The patient was undernourished, fairly well built, pallid, and appeared older than his stated age of 29 years. There was a generalized purpuric eruption, most marked over the lower extremities and characterized by innumerable petechiae and many purpuric maculae as large as 1 cm. in diameter. There were large scarred areas over the lower part of the left foreleg and ankle and over the dorsa of both feet, where the skin was thin, scaly, deeply pigmented, and fixed to the underlying tissues. The lymph nodes were not enlarged. In the right optic fundus there was a large, fresh hemorrhage and several areas of absorbing exudate. The nasal passages were obstructed with crusted blood and there was continuous oozing from the right nostril. The mouth was edentulous and there were numerous small hemorrhages in the oral and pharyngeal mucous membrane. The lungs and heart were within normal limits. The pulse rate was 100 per minute and the blood pressure was 150/95 mm. Hg. The peripheral arteries were soft and pulsated normally. The spleen descended two fingersbreadth below the left costal margin, but no other abdominal organs or masses were palpable. The right testicle was in the inguinal canal. Prolapsing internal hemorrhoids were found on rectal examination. The fingers were slightly clubbed and there was slight thoracic kyphosis, but the remainder of the skeletal system was normal. Examination of the nervous system revealed no abnormalities.

Laboratory Findings. The hematologic findings are given in Table I, and normal values for the hemostatic tests employed are given in Table II. There was a marked anemia, probably due to continuous blood loss. The leukocyte count varied between 2,900 and 6,400 per cmm. The differential count was normal except for a slight increase in the percentage of polymorphonuclear neutrophils. The platelet count varied between 80,000 and 250,000 per cmm. Furthermore, it was noted that the platelets were large, stained poorly, and did not contain granules. The bleeding time was markedly prolonged, the clot retraction very poor, and the capillary fragility definitely increased. The prothrombin concentration was slightly below normal on the patient's entry to the hospital and fell to 40 per cent of normal during the ensuing 3 weeks. It rapidly returned to normal following the administration of vitamin K. The coagulation time of the venous blood, tested at room temperature, was moderately prolonged when the patient was first observed and subsequently became markedly prolonged. The coagulation time of the venous blood at 37° C. was tested only during the last week of life when it was found to be moderately prolonged.

It should be pointed out that, while there is only a slight difference between the normal values for the coagulation time at room temperature and at 37° C., there is a marked difference between their pathologic ranges. In parallel tests done on the same blood specimens it has been found that coagulation time of 5 to 10 hours at room temperature will be reduced to 1 to 2 hours at 37° C.[44] The experimental observations relating to the coagulation defect were made on January 5 and 7, 1942, and are discussed below.

The urine was grossly bloody, specific gravity was 1.023, albumin was positive (3 plus). The stool gave a positive test for occult blood (4 plus). The plasma

TABLE I
Results of Hematologic Tests

Date	Hemoglobin in gm. per 100 cc.	Erythrocytes in millions per cmm.	Leukocytes per cmm.	Differential white blood cell count in per cent					Platelets per cmm.	Bleeding time in minutes
				Polymorphonuclear cells		Polymorphonuclear eosinophils	Lymphocytes	Monocytes		
				Fil.	Non-Fil.					
12-4-41	7.7	2.68	5300	60	4		20	16	80,000	
12-5-41									70,000	30
12-10-41									90,000	
12-14-41									100,000	
12-16-41	6.1	1.88	4300	74	8	1	10	7	180,000	
12-20-41			4600						170,000	
12-21-41									190,000	
12-23-41										
12-24-41	6.9	2.53	4300						160,000	10½
12-26-41	6.9	2.50	3900						170,000	
12-27-41	7.4	2.58	3200						120,000	
12-29-41	7.7	2.45	4400						120,000	
12-30-41	7.7	2.60	3100						230,000	30
12-31-41	8.4	2.74	3400						200,000	
1-2-42	8.4	3.01	3900						250,000	30
1-3-42	7.6	2.78	2900						200,000	
1-5-42	7.7	3.01	3700						160,000	
1-6-42	7.7	3.22	4500						180,000	30
1-7-42									100,000	
1-8-42	7.2	2.70	4900	46	35		11	8	140,000	

TABLE I—*continued*

Date	Coagulation time of venous blood at room temperature in minutes	Coagulation time of venous blood at 37°C. in minutes	Fluid volume of clot in per cent	Prothrombin concentration in per cent of normal	Capillary fragility in numbers of petechiae					Citrated whole blood transfusions in cc.
					Arm		Thigh			
					mm. Hg suction		mm. Hg suction			
					150	200	100	150	200	
12-4-41										
12-5-41	24		50	75	15	Shower*	Shower	Shower	Shower	300
12-10-41										500
12-14-41										500
12-16-41										
12-20-41										
12-21-41										500
12-23-41										500
12-24-41	42		44	40	2	2	1	Shower	Shower	
12-26-41										
12-27-41										500
12-29-41										
12-30-41	105		43	45†	1	4	6	Shower	Shower	
12-31-41										
1-2-42	175		43	70	0	0	Shower	Shower	Shower	
1-3-42										500
1-5-42		23½								
1-6-42	130		44	80	9	10	Shower	Shower	Shower	
1-7-42		25½								500
1-8-42	52	24½								500

* "Shower" indicates that the petechiae were too numerous to count accurately; usually from 50 to several hundred were present.

† Two mg. Symkamin (4 amino-2 methyl-1 naphthol) Parke, Davis & Co., administered intravenously on 12-30-41 and daily thereafter.

fibrinogen was 1.17 gm. per 100 cc. The serum calcium was 9.6 mg., serum phosphorus, 5.43 mg., and nonprotein-nitrogen of the blood, 32.9 mg. per 100 cc. The Wassermann and Kahn reactions of the blood were negative. The icterus index was 9 units and the intravenous hippuric acid test for liver function gave a normal value (1.09 gm.). The intravenous phenolsulfonphthalein test of kidney function showed 70 per cent excretion of the dye in 2 hours. The tuberculin (1:10,000) skin test was negative. The patient belonged to blood group A.

Course of Illness. The patient received 4,300 cc. of citrated blood by transfusion (Table I). Numerous thrombi developed in the vessels used for venipuncture. Between December 9 and December 29, 1941, the patient received roentgen irradiation of the spleen (a total of 1200 r. to each of two areas). Epistaxis continued to recur despite repeated nasal packing and cauterization of bleeding points in Kiesselbach's area. The urine and stool were grossly bloody throughout most of his hospital stay. On December 8th the right malar region became edematous and markedly tender. Roentgenograms showed complete opacity of the right antrum and ethmoid cells without evidence of bone destruction. The condition persisted for about a week and was interpreted as due to hemorrhage into the antrum. On December 19th the patient complained of sore throat and difficulty in swallowing, and he was found to have a large submucous hemorrhage in the posterior wall of the pharynx, extending down into the tissues of the neck. While this hemorrhage was resorbing, he began to have a daily temperature elevation, reaching a maximum of 41°C. (rectal) on December 22nd. Although no abnormal physical signs were detected in the chest, roentgenograms showed patchy areas of increased density throughout most of the right lung field. During the following 8 days a total of 42 gm. of sulfadiazine were administered orally and the temperature gradually returned to normal. On January 6, 1942, the patient complained of pain

TABLE II

Normal Values for Hemostatic Tests *

Test	Mean	Standard deviation	Normal range
Bleeding time (Ivy), in minutes	3.2	1.6	0 to 6.4
Coagulation time of venous blood at room temperature in minutes	8.9	2.7	3.5 to 14.3
Coagulation time of venous blood at 37°C. in minutes	7.5	1.4	4.7 to 10.3
Clot retraction. Fluid volume per cent of clot†	7.9	6.0	—4.1 to 19.9
Platelet count per cmm.	409,000	68,000	273,000 to 545,000
Prothrombin concentration (Quick) in per cent of normal			75 to 100
Capillary fragility (Dalldorf). Number of petechiae appearing on arm with 200 mm. Hg vacuum pressure			0 to 10

* The coagulation time at 37°C. was determined on a group of 40 normal subjects. All other tests were performed on a group of 64 normal subjects. (This is the same group used by us in previous analyses [49,50] except that in a more critical clinical analysis 36 subjects, formerly considered to be normal, were excluded because their normality was questioned. This resulted in no statistically significant differences in the values for the mean, standard deviation, or normal range.) The standard statistical method was used in setting up the limits of normality for the bleeding time, coagulation time, fluid volume of the clot, and platelet count. The limits of significance of the data were set at two standard deviations from the mean, thereby including approximately 96% of the observations. The mean is taken at the point of reference. All measures which are calculated were at least three times their sampling errors. The limits of normality for the prothrombin concentration and capillary fragility were arbitrarily set by direct observation. The prothrombin concentration in 91% of the observations fell between 75% and 100%. In the capillary fragility test not more than 10 petechiae appeared in 92% of the observations. The technics for the tests here employed are described in references 34, 43, 48, and 49.

† Formerly called the "Extracorpuscular volume per cent" of the clot.

in the right upper abdominal quadrant, which by the following day had extended into the right lower chest and was referred to the right shoulder. On the evening of January 10th the patient complained of marked headache over the vertex. His neck was stiff and painful on attempted flexion, but he had no other abnormal neurologic signs. By the following morning he was in coma and had moderate bilateral symmetric proptosis, and marked boggy edema of the entire scalp, nuchal region, forehead, eyelids, and tongue. At 2:00 P.M. lumbar puncture was performed. The initial pressure was greater than 1,000 cm. of water, and after removal of 70 cc. of grossly bloody fluid the pressure was 750 cm. of water. There was no immediate change in the patient's condition and he expired 1 hour later.

AUTOPSY FINDINGS

Autopsy was performed 2 hours after death. Post-mortem lividity had appeared, but rigor mortis was absent. The entire scalp was thickened, boggy, and edematous, and the coronal portion was infiltrated with blood. There was marked edema of the eyelids, the under side of the tongue, and the posterior portion of the neck. There was moderate symmetric proptosis of the eyes, which were deviated upwards and divergent.

There was a small area of hemorrhage in the fat of the anterior mediastinum. The right pleural cavity contained 750 cc. of yellow, turbid fluid. There were numerous subpleural hemorrhages, bilaterally. The largest (8 cm. in diameter) was beneath the right posterior basal parietal pleura and the pleural membrane adjacent to it was thickened. The right lung weighed 500 gm.; the left lung, 300 gm. The major bronchi and pulmonary vessels were normal. Both lungs were congested and edematous, but there was no gross hemorrhage or consolidation.

The peritoneal cavity was normal. A portion of the omentum was adherent to the gallbladder. The liver weighed 2,200 gm. The anterior edge was rounded and the cut surface pale. The gallbladder and bile ducts were normal. The spleen weighed 340 gm.; its capsule was reddish gray and slightly wrinkled; numerous large, white lymphoid follicles were visible on the cut surface. The splenic pulp was pale red and could be scraped readily from the cut surface. The pancreas was normal. The entire gastrointestinal tract was normal except for a few tiny, mucosal hemorrhages in the stomach. The kidneys each weighed 260 gm. The corticomedullary differentiation was indistinct. Numerous small (1 to 2 mm.) hemorrhages were present throughout the parenchyma and beneath the capsule. The renal pelves and calyces, ureters, bladder, and prostate gland were normal. The undescended right testicle was half the normal size.

The heart weighed 340 gm. and was normal except for hemorrhagic infiltration of the right auricular wall and numerous atheromatous

plaques in the coronary arteries, one of which, situated 1 cm. from the mouth of the left coronary artery, partially occluded its lumen. There were a few small, atheromatous plaques in the abdominal aorta.

The pituitary body, thyroid gland, and adrenal glands were normal. There was an irregular, small (0.5 cm.) polypoid mass, containing several small mucoid cysts, projecting from the left vocal cord. The mediastinal and aortic lymph nodes were moderately enlarged, soft and congested. The marrow of the ribs and lumbar spine and sternum appeared grossly normal.

The brain weighed 1,310 gm. The cerebral convolutions were flattened and the cerebellar tonsils were prominent. There was an extensive subarachnoid hemorrhage around the base of the brain with a small amount of blood over the cortex. No other abnormalities were noted in the brain, but both cavernous sinuses were completely filled with firm, adherent, thrombotic material. The venous sinuses at the base of the skull were partly occluded by similar thrombi.

Microscopic Examination

Only those tissues which showed histopathologic changes will be described in detail. The heart, liver, gallbladder, pancreas, gastroenteric tract, and thyroid, parathyroid, prostate, and thymus glands were normal.

The pulmonary alveoli contained large numbers of pigment-filled macrophages. In some there were masses of condensed, hyalinized fibrin with early organization and many were atelectatic. A section of the right posterior basal parietal pleura showed that the pleura, subpleural connective tissue, and adjacent muscle were edematous and infiltrated with red blood cells and masses of hyaline fibrin with early organization.

The epithelium of the larynx was elevated. In the submucosa there was extensive infiltration with fresh red blood corpuscles and masses of hyaline fibrin and one zone of vascular granulation tissue containing pigment-filled macrophages. A majority of the numerous large veins contained organizing thrombi.

The malpighian bodies of the spleen were not enlarged nor well outlined. In the walls and in the lumina of the sinuses, reticulo-endothelial cells and macrophages were unusually prominent, and in the follicles these cells had replaced most of the lymphocytes. Both the sinuses and intersinusoidal spaces contained a moderate amount of blood, many polymorphonuclear leukocytes, a few neutrophilic myelocytes and plasma cells, a rare megakaryocyte, but no nucleated red blood corpuscles. No phagocytosis was demonstrable.

In the kidneys the majority of the glomeruli were normal; some were partially or completely hyalinized; some presented pericapsular fibrin deposits; and a few showed epithelial or fibrous capsular crescents. The afferent arterioles of occasional glomeruli were filled with hyaline thrombi. There were numerous, small, interstitial hemorrhages both recent and old, and many tubules contained blood or serous fluid. Collections of interstitial lymphocytes and small calcium deposits were noted.

There were a few small hemorrhages in the submucosa of the bladder which was infiltrated with many large lymphocytes and macrophages and a smaller number of neutrophilic leukocytes and plasma cells. There was considerable tubular atrophy of the right testis; however, interstitial cells were present in normal numbers. The urethral submucosa was moderately infiltrated with lymphocytes, large macrophages, and neutrophilic leukocytes.

The pituitary gland showed moderate hemorrhage into the capsule and the posterior lobe.

There was a small, recent, cortical hemorrhage in one adrenal gland.

Epidermis from the ankle was normal. The dermis was composed of dense, hyalinized, acellular fibrous tissue containing scattered lymphocytes and pigment-filled macrophages.

Mediastinal, peri-aortic, and other lymph nodes had essentially the same histologic structure. The peripheral follicles were large and fairly distinct. Except for a rim of lymphocytes, they consisted of large numbers of reticulo-endothelial cells and macrophages, a few plasma cells, and many nuclear fragments. The sinuses were prominent and dilated, and there was proliferation of the lining reticulo-endothelial cells. In the sinusoids there were numerous large macrophages, many of which contained blood pigment, and fewer lymphocytes, mast cells, plasma cells, and eosinophilic and neutrophilic leukocytes.

The relative quantity of fat cells, and of erythropoietic and myelopoietic tissue in the bone marrow was normal (Fig. 1). Approximately 20 per cent of the megakaryocytes had large, well formed, vesicular, multilobar nuclei and abundant, finely granular, eosinophilic cytoplasm without pseudopods. There was moderate shrinkage of the cytoplasm and nucleus of about 40 per cent of the megakaryocytes, and the remaining 40 per cent consisted of irregular, shrunken, basophilic nuclear masses surrounded by extremely scanty cytoplasm. An average of one megakaryocyte was present per high-power field.

No histologic alteration of the central nervous system was noted except for the presence of red blood cells and blood-pigment-containing macrophages in the subarachnoid space.

The fibrous septa, nerves, and ganglia of the cavernous sinuses were infiltrated with blood which had become condensed and amorphous. A surrounding chronic inflammatory reaction had occurred. The venous channels were narrowed and almost all of them were filled with thrombi (Figs. 2 and 3). The older thrombotic masses were composed of hyalinized fibrin and red blood corpuscles. Many of these thrombi had undergone early organization. The most recently formed thrombi consisted of platelet masses containing leukocytes and erythrocytes (Fig. 4). There was no apparent primary alteration of the endothelium.

An atherosclerotic process with calcification had greatly narrowed the lumina of both branches of the left coronary artery. There was minimal atherosclerosis of the aorta. There was marked alteration of small arteries (50 to 200 μ) in the myocardium, lungs, kidneys, gallbladder, urinary bladder, spleen, and in the capsules of the pituitary and adrenal glands. Some of these vessels showed hyperplasia of the media while others presented a fibrous intimal thickening. An occasional vessel of this size had a hyalinized wall, but none contained thrombi. The arterioles were not altered.

Pathologic Diagnoses

(1) Primary thrombocytopenic purpura with hemorrhage in the subarachnoid space, in the fibrous septa and nerves and ganglia of the cavernous sinuses, and in the mediastinum, lungs, subpleural space, right auricle, kidneys, stomach, adrenal gland, vocal cord, scalp, and skin. (2) Thrombosis of the basilar and cavernous sinuses, and of veins in the arms and laryngeal submucosa. (3) Generalized arteriosclerosis with atherosclerosis of coronary arteries and aorta, and hyperplastic arteriosclerosis involving small arteries of the myocardium, lungs, gallbladder, and the capsules of the pituitary and adrenal glands.

Discussion

The Hemostatic Defect

The clinical manifestations of hemorrhagic diathesis in this patient were those commonly found in purpura haemorrhagica and the results of the hemostatic tests were characteristic of that condition; *i.e.*, a low platelet count associated with markedly prolonged bleeding time, diminished blood clot retraction, and increased capillary fragility. In addition, the coagulation time of the blood was markedly prolonged. The most probable cause of the coagulation defect was hypothromboplastinemia. However, detailed investigations were performed in order

to exclude all other known causes of delayed coagulation of the blood.

Hypocalcemia was readily eliminated as a diagnostic possibility by the finding of a normal concentration of the serum calcium and by the inability of added calcium chloride solution to shorten the coagulation time.

A defect in coagulation due to deficiency of fibrinogen was likewise excluded by the finding of a high plasma fibrinogen concentration and by the appearance of ample quantities of formed fibrin in whole blood or plasma clots.

The initial prothrombin concentration was at the lower limit of normal and dropped to 40 per cent of normal during the ensuing 3 weeks. This possibly was due to continued blood loss and to specific dietary deficiency. It rapidly returned to normal following the administration of synthetic vitamin K. The fluctuations in the prothrom-

TABLE III

Coagulation Times of the Blood of W. J. F. Following the Addition of Protamine

Added protamine solution	Coagulation time of 2 cc. blood specimens of W. J. F.'s blood at 37°C.
(mg.*)	(minutes)
0.00	21
0.001	22
0.005	27
0.010	31.5
0.050	52.5
0.100	120

*Each concentration made up in 0.1 cc. of 0.85% NaCl solutions.

bin concentration appeared to bear no relationship to the prolonged coagulation time and, furthermore, the prothrombin concentration was at no time low enough to account for the delayed coagulation of the blood.[34-39]

Coagulation defects due to the circulation of anticoagulant substances in the blood are rare. A moderately prolonged coagulation time, presumably due to retention of toxic substances by the diseased kidneys, is sometimes found in severe uremia. In this patient there was no evidence of renal failure and the concentration of nonprotein nitrogen of the blood was normal.

The coagulation time can be markedly prolonged by the intravenous administration of heparin, and the anticoagulant effect of heparin can be neutralized by the addition of protamine to the blood.[40,41] The possibility that the coagulation defect in this patient might be due to an excess of heparin in the blood was eliminated by the addition of protamine to his blood *in vitro* (Table III). The prolonged coagulation time was not shortened by this procedure.

A prolonged coagulation time due to an unidentified circulating anticoagulant was recently reported by Lozner, Jolliffe and Taylor.[42] The plasma of their patient produced a marked prolongation of the coagulation time of normal blood when added in ratios of 1:10 and 1:20. In our patient no significant anticoagulant effect could be demonstrated by similar tests (Table IV). However, these experiments do not completely exclude the possibility of the presence of a circulating anticoagulant. If such an anticoagulant were present in a relatively weak concentration, its effect might remain undetected by the technic employed.

TABLE IV

Coagulation Times of the Blood of a Normal Subject Following the Addition of Graded Quantities of the Plasma of W. J. F.

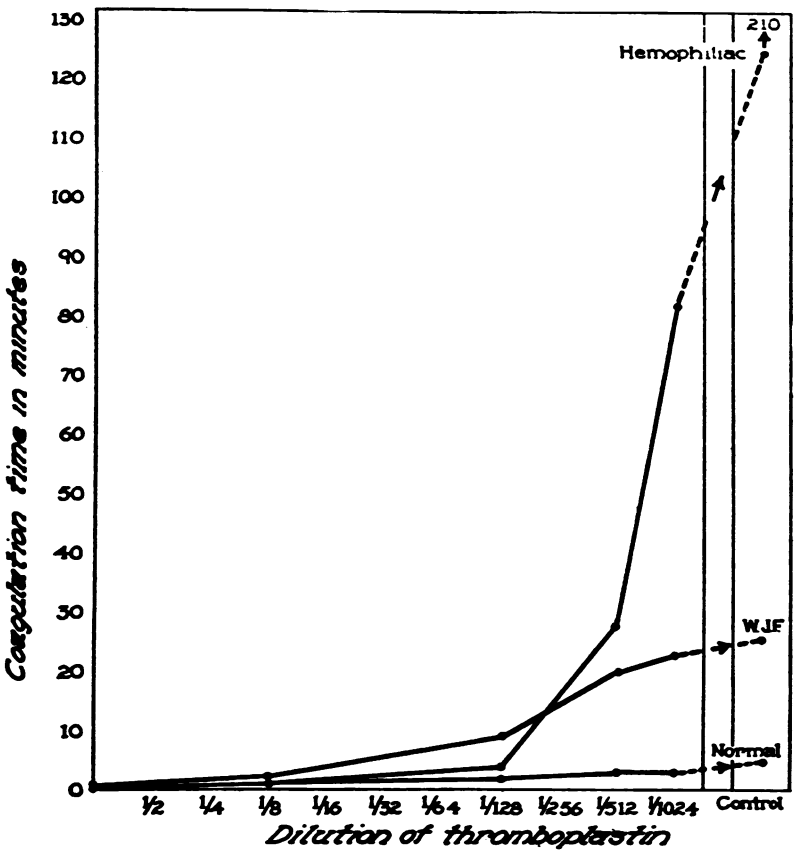
Added citrated plasma of W. J. F.	Coagulation time of 2 cc. specimens of normal blood at 37°C.
(*cc.*)	(*minutes*)
0	8.5
0.02	10
0.05	9
0.10	11.5
0.20	11

The possibility of the presence of both thrombocytopenic purpura and hereditary hemophilia in this patient seemed remote since his clinical history was not that of hemophilia and his family history gave no support to such a diagnosis. The question of an acquired abnormality similar to that of hemophilia was considered. The exact nature of the hemophilic defect is disputed. Quick [43] has recently defended the traditional hypothesis that it is a pure thromboplastin deficiency caused by decreased rate of lysis of platelets. This view is perhaps supported by the observation that the prolonged coagulation time of hemophilic blood can be shortened to normal either by the addition of a minute quantity of tissue extract containing thromboplastin, or by the addition of a small amount of normal blood or plasma. On the other hand, the group working at the Thorndike Memorial Laboratory believe that the platelets are normal in hemophilia and that the defect in coagulation is due to the absence of an activator which is present in the globulin fraction of normal blood.[44-47]

We performed a number of experiments to determine if a coagulation defect of the blood similar to that of hemophilia was present in this patient. In Text-Figure 1 are given the results of experiments which were devised to compare the coagulation times of the *whole blood* of the patient with those of a known hemophiliac * after the addi-

* The hemophiliac was patient L. T., whose case has been described in detail.[20]

tion of progressively decreasing concentrations of thromboplastin solution.* A similar series of tests, the results of which are given in Text-Figure 2, was performed in order to compare the *plasma* coagulation times of the patient with those of a hemophiliac after the addition of thromboplastin solutions.†



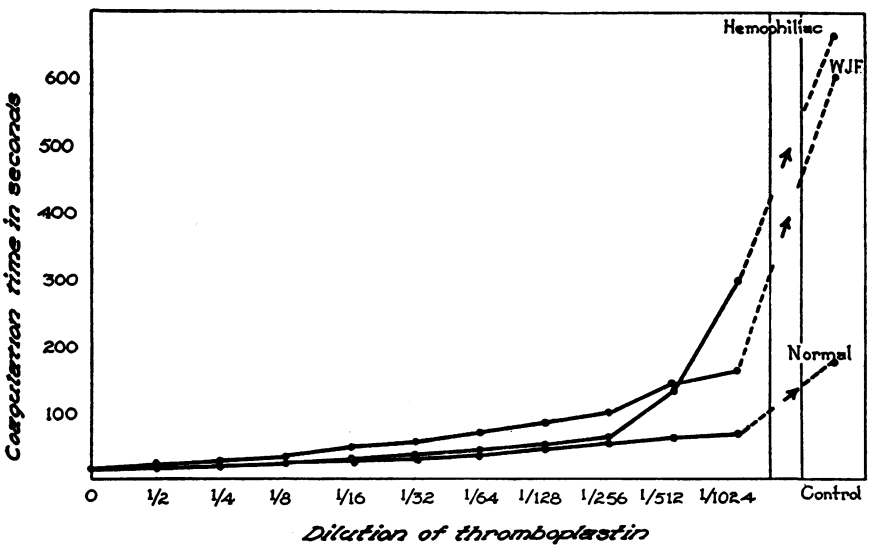
Text-Figure 1. The effect of progressively decreasing concentrations of thromboplastin solution on the coagulation time of the whole blood of a normal subject, a known hemophiliac, and of the patient W. J. F.

In full strength or in moderate dilution, the thromboplastin solution caused a greater reduction in the coagulation time of the hemophilic blood than of the patient's blood. With greater dilution of the thromboplastin solution there was less effect on the coagulation time of either

* The thromboplastin solution was prepared as for the prothrombin test according to the method of Quick.[48] The tests were performed at 37° C. in 12 by 100 mm. tubes. 0.1 cc. of progressive dilutions of the thromboplastin solution was added to 2 cc. specimens of blood. The tubes were inverted once for mixing.

† The tests were performed in the same manner as the Quick prothrombin test[48] except that a series of dilutions of the thromboplastin solution was used for testing.

of the bloods and they approached the control time in which physiologic saline solution was substituted for thromboplastin. Similar results were obtained in the tests performed on the respective plasmas. The lessened coagulative activity of the concentrated thromboplastin solutions on the patient's blood or plasma was probably due to the slightly diminished prothrombin concentration in his blood. On the basis of their reactions to thromboplastin, one would not be able to distinguish between the coagulation defect of this patient and that of a hemophiliac with a similar degree of hypoprothrombinemia. However, in another



Text-Figure 2. The effect of progressively decreasing concentrations of thromboplastin solution on the coagulation time of recalcified plasma of a normal subject, a known hemophiliac, and of the patient W. J. F.

series of experiments in which the coagulation times of the whole blood of the patient were compared to those of the hemophiliac after the addition of graded quantities of normal blood (Table V) and plasma (Table VI), a difference between the two bloods was clearly demonstrated. The same quantities of normal blood or plasma which produced a marked reduction in the coagulation time of hemophilic blood had little effect on the coagulation time of the patient's blood. Furthermore, the transfusion of whole blood did not shorten the coagulation time of the patient's blood in a manner comparable to that usually seen in hemophilia.

Unfortunately, with the present available methods, it is impossible to measure the thromboplastin content of human blood, and therefore one cannot prove that a condition of hypothromboplastinemia exists. It seems reasonable to assume that it is present, however, when, as in

the present case, (1) there is a significant degree of thrombocytopenia, (2) the structure of the platelets is altered, (3) the coagulation defect is corrected by the addition of thromboplastin, and (4) all other known causes of delayed blood coagulation have been excluded.

TABLE V

Coagulation Times of the Blood of W. J. F. and of a Known Hemophiliac before and after the Addition of Graded Quantities of Normal Human Blood

Added citrated normal blood	Coagulation time of 2 cc. blood specimens at 37°C.	
	Hemophiliac	W. J. F.
(*cc.*)	(*minutes*)	(*minutes*)
0 (control)	120	23.5
0.02	24	17
0.05	19.5	16
0.10	13	19
0.20	11	20

If it is assumed that the cause of the delayed coagulation time in this patient was hypothromboplastinemia due to deficient platelet numbers and function, then the results of these experiments would tend to support the belief of the Thorndike group that the substance in normal blood which is effective in shortening the coagulation time of hemophilic blood is not thromboplastin but some other plasma constituent.

The Thrombotic Features

Thrombosis may be caused by alteration in the diameter of the vessel lumen with consequent changes in the blood current, by damage to the intima of blood vessels, and by physicochemical changes in the blood. Alterations in the blood itself, which, under certain circumstances, may contribute to the formation of thrombi, include increases in the number or agglutinating power of the platelets, the coagulability of the blood, the quantity of the globulin-fibrinogen fraction of the blood proteins, and increased liberation of thromboplastin from disintegrated blood and tissue cells.

TABLE VI

Coagulation Times of the Blood of W. J. F. and of a Known Hemophiliac before and after the Addition of Graded Quantities of Normal Human Plasma

Added citrated normal human plasma	Coagulation time of 2 cc. blood specimens at 37°C.	
	Hemophiliac	W. J. F.
(*cc.*)	(*minutes*)	(*minutes*)
0.0 control	120	25
0.02	25	19
0.05	15	20.5
0.10	14.5	22
0.20	15	25

Despite the presence of a marked hemorrhagic tendency, the patient developed thrombosis in the cavernous and basilar sinuses, in the veins of the arms, and in the laryngeal submucosa. It is difficult to determine the cause of these thrombotic episodes. Because of the marked bleeding tendency, it seems logical to assume that spontaneous hemorrhages into the septa of the cavernous sinuses resulted in narrowing of the lumina, producing endothelial damage with consequent thrombosis. The partial thrombosis of the basilar sinuses may have been caused by propagation from the cavernous sinuses. On the other hand, the original thrombosis may have occurred in the nasal tract following treatment of epistaxis, and may have been propagated thence to the cavernous sinuses.

The thrombi noted in the veins of the submucosa of the larynx were probably secondary to a large hemorrhage which had occurred several weeks before death. Phlebothrombosis in the arms occurred only along the course of veins traumatized by venipuncture. No primary alteration in the endothelium of arteries or veins could be detected in any of the material studied.

Although the primary cause of thrombosis is not discoverable in this case, the laboratory data give evidence that the blood platelets failed to function properly in the process of blood clot retraction; [48,49] they failed to assist in maintaining capillary continuity; [5] and they did not supply enough thromboplastin to ensure an efficient coagulation of the blood.

Summary

A case of primary thrombocytopenic purpura is presented, in which there was a markedly prolonged coagulation time of the blood in addition to the usual findings of prolonged bleeding time, diminished blood clot retraction, and increased capillary fragility. The patient had had frequent epistaxis and had bruised easily since childhood, and for 1 year before death these symptoms had increased in frequency and severity and were associated with the appearance of numerous petechial hemorrhages on the lower extremities. While in the hospital the patient suffered from a generalized purpuric eruption, epistaxis, retinal hemorrhages, bleeding into the oral and pharyngeal mucous membranes, bleeding hemorrhoids, bleeding into the right maxillary sinus, subpleural hemorrhages, a large submucous hemorrhage into the posterior wall of the pharynx, gross hematuria, and a large meningeal hemorrhage. Terminally, he presented the signs of bilateral cavernous sinus thrombosis.

The post-mortem examination disclosed: (1) Hemorrhages in the subarachnoid space; in the fibrous septa, nerves and ganglia of the

cavernous sinuses; and in the mediastinum, lungs, subpleural space, right auricle, kidneys, stomach, adrenal gland, vocal cord, scalp, and skin. (2) Thrombosis of the basilar and cavernous sinuses, and of veins in the arms and laryngeal submucosa. (3) Generalized arteriosclerosis with atherosclerosis of coronary arteries and aorta, and hyperplastic arteriosclerosis involving small arteries of the myocardium, lungs, gallbladder, and of the capsules of the pituitary and adrenal glands.

The prolonged coagulation time was thought to be due to hypothromboplastinemia caused by deficient platelet numbers and function because: (1) there was a significant degree of thrombocytopenia, (2) the structure of the platelets was altered, (3) the coagulation defect was corrected by the addition of thromboplastin, and (4) all other known causes of delayed blood coagulation were eliminated. The coagulation defect differed from that found in hemophilia in that it was not corrected by the addition of small amounts of normal blood or plasma *in vitro* nor by the transfusion of whole blood *in vivo*.

The cavernous sinus thrombosis appeared to be due either to propagation of a thrombus from the nasal submucosa, or to spontaneous hemorrhages into the septa of the cavernous sinuses with resulting endothelial damage and narrowing of the lumina.

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REFERENCES

1. Aggeler, P. M. Heparin and dicumarol—anticoagulants. Their prophylactic and therapeutic uses. *California & West. Med.*, 1946, **64**, 71–77.
2. Tocantins, L. M. Experimental thrombopenic purpura; cytological and physical changes in the blood. *Ann. Int. Med.*, 1936, **9**, 838–849.
3. Unpublished data. (For statistical method: Yule, G. U., and Kendall, M. G. An Introduction to the Theory of Statistics. C. Griffin & Co., London, 1940, ed. 12, p. 44.)
4. Evans, W. H. The blood changes after splenectomy in splenic anemia, purpura haemorrhagica and acholuric jaundice, with special reference to platelets and coagulation. *J. Path. & Bact.*, 1928, **31**, 815–832.
5. Tidy, H. L. The haemorrhagic diathesis. *Proc. Roy. Soc. Med.* (Sect. Med.), 1927–28, **21**, 33–52.
6. Washburn, A. H. Splenectomy in thrombocytopenic purpura. Report of three cases. *J. A. M. A.*, 1930, **94**, 313–317.
7. Guller, E. I., and Lawrence, J. S. Idiopathic thrombopenic purpura. *Ann. Int. Med.*, 1930–31, **4**, 1535–1544.
8. Mettier, S. R., and Stone, R. S. The effect of roentgen ray irradiation on platelet production in patients with essential thrombocytopenic purpura haemorrhagica. *Am. J. M. Sc.*, 1936, **191**, 794–807.
9. Marzollo, E. Sindrome di diatesi emorragica del gruppo Werlhof con atipico reperto ematologico. *Haematologica*, 1938, **19**, 923–937.
10. Aubertin, C., and Lafon, J. Incoagulabilité plasmatique dans le purpura. *Paris méd.*, 1940, **2**, 381–383.

11. Mettier, S. R. Central nervous system complications arising from diseases of the blood forming tissues. *J. Nerv. & Ment. Dis.*, 1944, **99**, 758–767.
12. Finesilver, B., and Boyd, L. J. Cerebral hemorrhage in purpura hemorrhagica. Report of a case. *J. Am. Inst. Homeop.*, 1934, **27**, 129–131.
13. Spörl, H. J. Mitteilung über Werlhofsche Krankheit und Hirnblutung. *Jahrb. f. Kinderh.*, 1935, **146**, 39–42.
14. Traub, E. Über das Vorkommen von Gehirnblutungen beim Morbus Werlhof. *Ztschr. f. Kinderh.*, 1936–37, **58**, 67–72.
15. Laignel-Lavastine and Cachin, Y. Purpura avec hémiplégie double chez une hyperthyroïdienne. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1940, **56**, 411–416.
16. Alpers, B. J., and Duane, W., Jr. Intracranial hemorrhage in purpura hemorrhagica. *J. Nerv. & Ment. Dis.*, 1933, **78**, 260–273.
17. Ackman, F. D. A case of purpura haemorrhagica: death due to cerebral haemorrhage. *Canad. M. A. J.*, 1925, **15**, 186–187.
18. Longcope, W. T. Cerebral and spinal manifestations of purpura haemorrhagica. *M. Clin. North America*, 1919, **3**, 279–300.
19. Cabot case no. 18072. A case of rapidly progressive hemiplegia. *New England J. Med.*, 1932, **206**, 356–357.
20. Garvey, P. H., and Stephens, D. J. Purpura hemorrhagica with intracranial hemorrhage. *New York State J. Med.*, 1936, **36**, 97–101.
21. Geiger, A. J. Purpura haemorrhagica with cerebrospinal hemorrhage. Report of two cases. *J. A. M. A.*, 1934, **102**, 1000–1001.
22. Gitt, J. J., and Weiss, E. J. Subarachnoid hemorrhage as a primary manifestation of thrombocytopenic purpura; splenectomy and recovery. *J. Missouri M. A.*, 1940, **37**, 73–75.
23. Meyer, J., and Parker, M. Subarachnoid hemorrhage in a case of purpura hemorrhagica. *M. Clin. North America*, 1930, **13**, 1205–1209.
24. Lizier, E. Di un caso di morbo di Werlhof (trombocitopenia essenziale) con emorragie meningeali, operato di splenectomia. *Riforma Med.*, 1932, **48**, 552–557.
25. Dunlop, H. A. "Essential" haemorrhagic purpura, with transient mid-brain symptoms. *Practitioner*, 1934, **132**, 709–711.
26. Spangenberg, J. J., Márquez, J. F., and Falco, L. N. M. Nanismo hipofisario y enfermedad de Werlhof a forma crónica intermitente. *Rev. Asoc. méd. argent.*, 1933, **47**, 3536–3543.
27. Michail, D. Bilateral atrophy of optic nerve as sequel of thrombolytic purpura. *Rev. san. mil., Bucuresti*, 1936, **35**, 384–385.
28. Olsen, C. W., and Comstock, D. D. Purpura hemorrhagica, complicated by hematomyelia. Report of a case. *Bull. Los Angeles Neurol. Soc.*, 1937, **2**, 135–140.
29. Evang, K. A case of essential thrombopenia (morb. Werlhof) with haematomyelia. *Acta psychiat. et neurol.*, 1928, **3**, 7–22.
30. Aggeler, P. M., and Lucia, S. P. The neurologic complications of hemophilia. *J. Nerv. & Ment. Dis.*, 1944, **99**, 475–500.
31. Geiger, A. J., and Evans, A. G. Atypical hereditary hemorrhagic syndromes, *Internat. Clin.*, 1938, **2**, 135–157.
32. Tschopp, W. Purpura mit hämophilieartiger vorübergehender Gerinnungsstörung. *Ztschr. f. klin. Med.*, 1937, **132**, 293–307.
33. Welt, B., and Kasnetz, J. Thrombopenic purpura as complication. *Arch. Otolaryng.*, 1938, **27**, 732–735.
34. Lucia, S. P., and Aggeler, P. M. A clinical evaluation of the bleeding tendency. *Clinics*, 1942, **1**, 414–432.

35. Aggeler, P. M., and Lucia, S. P. The nature and treatment of the bleeding tendency in obstructive jaundice and diseases of the liver. *Clinics*, 1942, 1, 433–447.
36. Aggeler, P. M., Lucia, S. P., and Goldman, L. Effect of synthetic vitamin K compounds on prothrombin concentration in man. *Proc. Soc. Exper. Biol. & Med.*, 1940, 43, 689–694.
37. Lucia, S. P., and Aggeler, P. M. The influence of liver damage on the plasma prothrombin concentration and the response to vitamin K. *Am. J. M. Sc.*, 1941, 201, 326–340.
38. Aggeler, P. M., and Lucia, S. P. The bleeding tendency in diseases of the liver and biliary passages. *Acta med. Scandinav.*, 1941, 107, 179–226.
39. Aggeler, P. M., Lucia, S. P., and Fishbon, H. M. Purpura due to vitamin K deficiency in anorexia nervosa. *Am. J. Digest. Dis.*, 1942, 9, 227–229.
40. Chargaff, E., and Olson, K. B. Studies on the chemistry of blood coagulation. VI. Studies on the action of heparin and other anticoagulants. The influence of protamine on the anticoagulant effect *in vivo*. *J. Biol. Chem.*, 1937–38, 122, 153–167.
41. Chargaff, E. Studies on the chemistry of blood coagulation. VII. Protamines and blood clotting. *J. Biol. Chem.*, 1938, 125, 671–676.
42. Lozner, E. L., Jolliffe, L. S., and Taylor, F. H. L. Hemorrhagic diathesis with prolonged coagulation time associated with a circulating anticoagulant. *Am. J. M. Sc.*, 1940, 199, 318–327.
43. Quick, A. J. The Hemorrhagic Diseases and the Physiology of Hemostasis. C. C. Thomas, Springfield, Ill., 1942, 340 pp.
44. Patek, A. J., and Stetson, R. P. Hemophilia. I. The abnormal coagulation of the blood and its relation to the blood platelets. *J. Clin. Investigation*, 1936, 15, 531–542.
45. Patek, A. J., and Taylor, F. H. L. Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. *J. Clin. Investigation*, 1937, 16, 113–124.
46. Pohle, F. J., and Taylor, F. H. L. The coagulation defect in hemophilia. The effect in hemophilia of intramuscular administration of a globulin substance derived from normal human plasma. *J. Clin. Investigation*, 1937, 16, 741–747.
47. Lozner, E. L., Kark, R., and Taylor, F. H. L. The coagulation defect in hemophilia: the clot promoting activity in hemophilia of Berkefelded normal human plasma free from fibrinogen and prothrombin. *J. Clin. Investigation*, 1939, 18, 603–608.
48. Aggeler, P. M., Lucia, S. P., and Hamlin, L. M. Blood clot retraction. I. Measurement of the extracorpuscular volume of the clot. *J. Lab. & Clin. Med.*, 1942–43, 28, 89–97.
49. Lucia, S. P., Aggeler, P. M., and Hamlin, L. M. Blood clot retraction. II. The significance of the extracorpuscular volume of the clot and its clinical application. *Am. J. M. Sc.*, 1942, 204, 507–516.
50. Lucia, S. P., and Aggeler, P. M. Simple easy bruisability: a pseudo-hemorrhagic diathesis of probable endocrine origin. *J. Clin. Endocrinol.*, 1942, 2, 457–459.

[*Illustrations follow*]

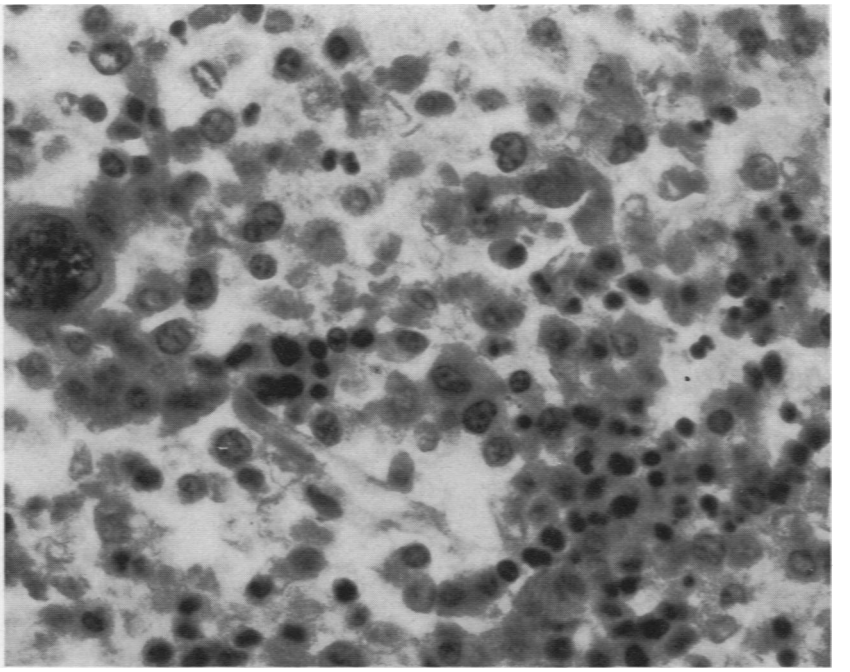
DESCRIPTION OF PLATES

PLATE 239

FIG. 1. Bone marrow of lumbar spine. × 650.

FIG. 2. Cavernous sinus showing thrombosis with organization. × 120.

1



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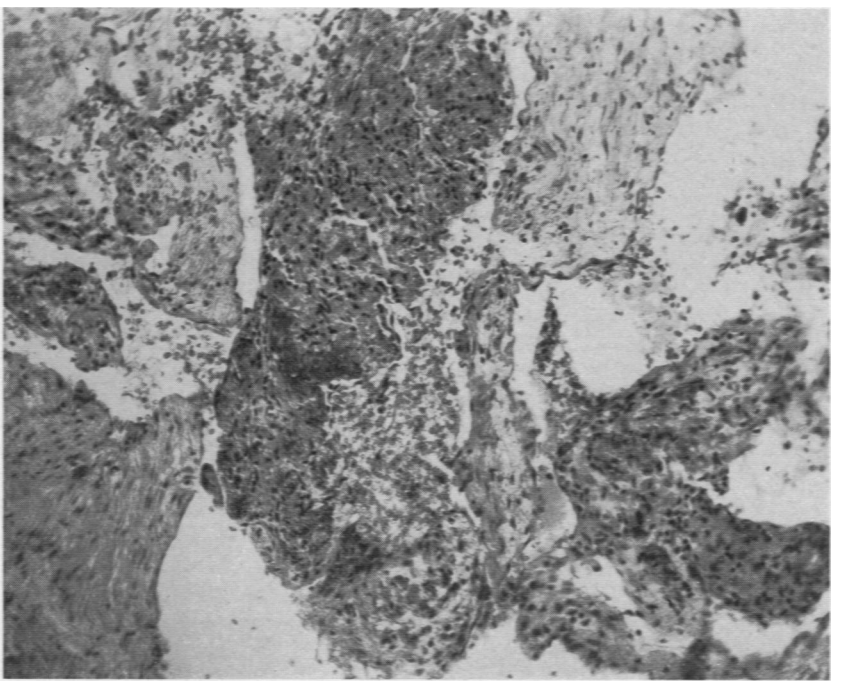
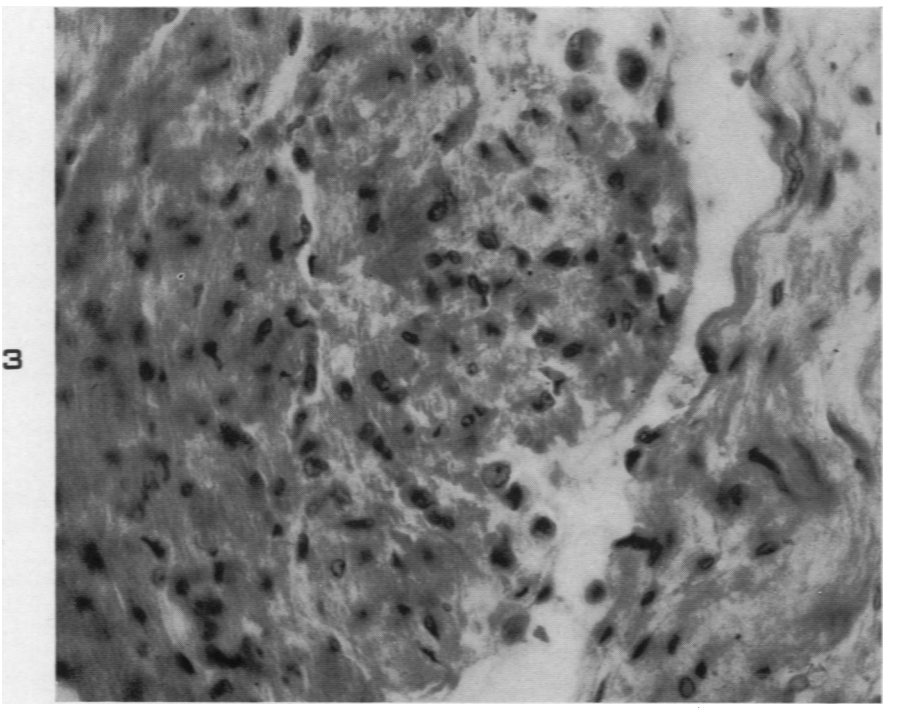


PLATE 240

FIG. 3. Higher magnification of one area shown in Figure 2. Late organization of the thrombus. × 500.

FIG. 4. Portion of thrombus from cavernous sinus showing occasional leukocytes and erythrocytes, separated by granular masses of platelets. × 750.



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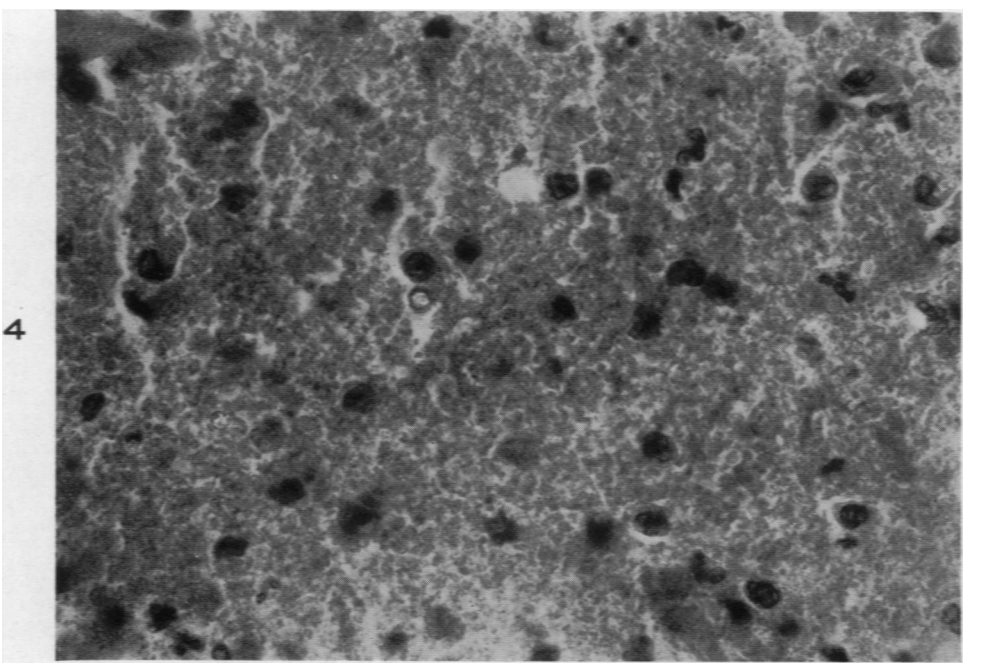

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