·MEDICINE
Vol. 45, No. 2

Printed in U.S.A.

THROMBOTIC THROMBOCYTOPENIC PURPURA: REPORT OF 16 CASES AND REVIEW OF THE LITERATURE[1, 2]

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I. INTRODUCTION

Two hundred seventy-one cases of thrombotic thrombocytopenic purpura have been recorded in the medical literature since the initial description by Moschcowitz in 1925.[5] Following the publication of his paper entitled "An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of Terminal Arterioles and Capillaries; an Undescribed Disease" (139), eleven years elapsed before Baehr, Klemperer, and Schifrin reported four similar cases (9). Since then, this entity has been called Moschcowitz's disease or syndrome (15), thrombotic thrombocytopenic purpura (186), thrombotic microangiopathic hemolytic anemia (194), thrombocytic acro-angiothrombosis (75), disseminated arteriolar and capillary thromboses (89), platelet thrombosis syndrome (12), thrombohemolytic thrombocytopenic purpura (2), and a variety of other names (7, 35, 79). It is now commonly referred to as thrombotic thrombocytopenic purpura (TTP).

Thrombotic thrombocytopenic purpura is usually described as a triad consisting of thrombocytopenic purpura, hemolytic anemia, and neurologic manifestations. As has been emphasized previously (122), fever and evidence of renal disease are almost invariably present, and the syndrome should be considered as a pentad of clinical findings. Diagnostic confirmation of this syndrome requires the histologic demonstration of the characteristic pathologic lesion consisting of widespread hyaline occlusion of terminal arterioles and capillaries. Most cases accepted for review in the present report had histologic confirmation of their disease. In 20 cases (5, 17, 31, 60, 61, 62, 111, 116, 120, 121, 140, 144, 173, 180, 182, and Cases VIII and XVI) no confirmation was obtained; however, the respective authors felt that each case was typical and we accepted it if the triad of TTP was present.

The 16 cases of TTP from the Presbyterian Hospital are presented in tabular form (Table I). Thirteen of these cases have been published previously (145, 148, 163, 211). The four cases most recently encountered will be described in detail.

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[5] The reported cases are those cited in the 185 references *not* preceded by an asterisk.

TABLE I

Clinical Features in 16 Cases of TTP at CPMC

Case No.	Reference	Age & sex	Chief complaint and duration	Antecedent history	Symptoms and signs on admission															Laboratory findings												Course	Duration hospitalization	Steroid therapy	Autopsy
						Anemia				Bleeding				Neurologic												Urinalysis										
					Fever	Weakness	Pallor	Jaundice	Petechiae	Ecchymoses	Retinal	Mucosal	Headache	Aphasia	Confusion	Paresis	Visual	Abd. pain	Hb g/100 ml	WBC/mm³ × 10³	Reticulocyte %	Normoblasts per 100 WBC	Bilirubin mg/100 ml	Platelets/mm³ × 10³	Protein	WBC	RBC	Casts	BUN mg/100 ml						
I	211	21 M	Anemia; 6 mo.	Flu-like syndrome	+	+	+	+	+		+	+	+						3.8	4.9	43.0	2	4.0	5		+	+	+	73	Severe anemia and death from sepsis	3 mo.	No	+
II	211	44 M	Headache, aphasia; 10 days	Lead exposure	+	+	+					+	+	+	+			+	6.3	5.8	19.0	2		46	+		+	+	25	Purpura, seizures, coma, death	5 days	No	+
III	211	32 F	Vomiting, abdominal pain; 4 days	Dye exposure	+	+	+	+	+	+		+			+				7.0	21.0		3		50	+		+	+	48	Hemiparesis, coma, death	1 day	No	+
IV	211	16 F	Hemiparesis; 10 days	None	+											+	+		9.0	5.7				142					12	Paresis cleared; seizures and coma preceded death	7 wk.	No	+
V	211	40 F	Intermittent confusion, aphasia; 10 wk.	Otitis; penicillin Rx	+	+		+			+	+	+	+	+				7.3	6.5	10.0	4	1.0	10	+		+		19	Purpura, paresis, aphasia, coma, death	4 wk.	No	+
VI	211	44 M	Variable neurologic symptoms, hypertension; 7 yrs.	Rabies Rx as a child	+								+			+			14.0	7.1					+	+	+	61	Fever, death	6 days	No	+
VII	211	37 F	Confusion, abdominal pain; 3 mo.	Hypertension	+	+			+	+					+		+	+	8.6	35.0	6.8		1.0	32	+		+		31	Fever, heart failure, coma, death	3 days	No	+
VIII	145	47 F	Headache, aphasia; 14 days	None	+					+			+	+	+				4.2	9.0	14.0		0.9	35						Disoriented, hemiparesis, coma, and death	7 wks.	Cortisone 300 mg per day	Not done
IX	145	44 M	Nausea, vomiting, abdominal pain; 1 wk.	Heroin addiction	+			+						+	+	+			8.5	12.0	16.0	2	4.7	24	+		+			Varying mental state, seizures, coma, and death	4 days	No	+
X	145 163	32 F	Fever, malaise, fatigue; 1 wk.	6 mo. pregnant	+	+	+						+				+		8.4	17.0	7.0	15	0.3	32	+	+	+		49	Miscarriage; purpura, coma and death	4 days	No	+

XI	145	55 F	Vomiting, blurred vision; 5 days	Hypertension	+										+		8.5	12.0	15.0	2		29	+	+	+	+	62	Varying mental state, seizures, coma, and death	8 days	Hydrocort. 100 mg. /day	+
XII	145 163	31 F	Cystitis, back pain, gum bleeding; 1 wk.	8 mo. pregnant. Sulfa Rx; penicillin Rx for syphilis							+						7.9	22.0	7.2	3	2.5	42	+		+		42	Miscarriage; fever, purpura, melena aphasia, coma, and death	7 days	Prednisone 500 mg per day	+
XIII	—	33 F	Weakness, nausea, headache, fever; 11 days	5 mo. pregnant. Scalp rash due to hair dye	+	+		+	+	+							+	6.0	14.0	13.0	37	3.9	60	+	+	+	+	10	Aphasia, seizures, coma, and death	1 day	No	+
XIV	148	35 F	Aphasia, hemiparesis; 18 mo.	6 mo. pregnant		+	+	+	+	+			+		+	+	+	8.3	15.0	8.4		1.8	26	+	+	+		65	Fever, oliguria, azotemia, melena, coma, and death	11 days	Prednisone 60 mg/day	+
XV	—	43 M	Headache; 10 days	Raynaud's syndrome 1 yr.	+			+				+	+	+	+		+	6.3	14.0	19.3	15	4.5	19			+		18	Fever, hemiparesis, tetany, and death	3 days	Prednisone 100 mg per day	+
XVI	—	28 F	Ecchymoses, hematuria, fatigue, jaundice; 1 mo.	Hair dye exposure		+		+		+	+	+			+		+	11.0	10.0	14.0	15	3.7	25	+	+	+			Periodic confusion, delirium, rapid improvement, and recovery.	7 days	Prednisone 60 mg per/day	Alive

II. CASE REPORTS

Case XIII. E. W., a 33-year-old Jamaican-born Negro, was transferred from another hospital to the Columbia-Presbyterian Medical Center (CPMC) on July 30, 1960. Five months prior to admission, she developed a scalp rash after using a hair dye. This progressed to a generalized maculopapular eruption which cleared only after three months of dermatologic remedies. Alopecia had developed. One month prior to admission, she presented with a 5-month history of amenorrhea. There had been three prior spontaneous abortions. Three weeks prior to admission, she developed abdominal cramps and vaginal bleeding. A dilatation and curettage were done and the currettings were reported to show products of conception. Eleven days prior to admission to the other hospital, she developed weakness, nausea, headache, and fever. While there, she developed jaundice and purpura and she was then transferred to the CPMC. On admission, the blood pressure was 140/80 mmHg; pulse, 110/min; respiration, 16/min; and temperature, 102°F. Jaundice, petechiae, and ecchymoses were noted. The fundi were normal. The liver and spleen were not felt. She was responsive but confused; there were no focal neurologic signs. Hemoglobin was 6.0 g/100 ml; hematocrit, 18%; RBC, 1.8 million/mm^3; WBC, 14,000/mm^3 with a normal differential; and anisocytosis, poikilocytosis, hypochromia, microcytosis, and macrocytosis, as well as target cells and basophilic stippling were noted. The ESR was 35 mm/hr. There were 37 normoblasts per 100 white cells. Reticulocyte count was 13% and platelet count was 60,000/mm^3. The serum was red and gave a 4+ guaiac reaction. Bone marrow examination revealed erythroid hyperplasia and numerous megakaryocytes. There was 4+ proteinuria and occasional white cells, red cells, and granular casts were seen. Clotting time, clot retraction, and prothrombin time were normal. The Coombs test was negative. Bilirubin was 3.9 mg/100 ml, mostly indirect. Alkaline phosphatase, thymol turbidity, and cephalin flocculation were normal. The total serum protein was 6.4 g/100 ml with an A/G ratio of 3.8/2.6 g/100 ml; 2-hr post-prandial sugar, 125 mg/100 ml; and BUN, 10 mg/100 ml. The cerebrospinal fluid showed 16 RBC/mm^3 and protein was 46 mg/100 ml.

She was treated with transfusions and antibiotics. Shortly after admission, aphasia and, later, coma developed. She had recurrent grand mal seizures, the pupils dilated, and she expired the day after admission. Prednisone, 100 mg, was given on the last day of life.

Post mortem examination showed hyaline thromboses of the vessels of heart, lungs, pancreas, kidneys, adrenals, spleen, nodes, thymus, bone marrow, gastrointestinal tract, thyroid, cerebrum, brain stem, cerebellum, and pituitary. No massive intracranial hemorrhage was noted. A chromophobe adenoma of the pituitary was found. Fibrous thickening of the mitral valve was seen. Review of the endometrial curettings revealed no diagnostic changes.

Case XIV.[6] M.N., a 35-year-old white woman in the sixth month of pregnancy, was admitted to CPMC on July 6, 1962, because of aphasia and right hemiparesis. Eighteen months prior to admission, left homonymous scintillating scotomata lasting one to two hours and occurring three times per week were noted by the patient. At that time, she was rejected as a blood donor because of anemia. Six months prior to admission, she observed a purpuric rash on her arm and experienced aching pain of her hands during housework. There were episodes of crushing, substernal chest pain, lasting one to two hours, accompanied by nausea, diaphoresis, and weakness. Two months prior to admission, she suddenly developed a left hemiparesis and hemihypesthesia, but this cleared completely in one hour. Two weeks later, she began to have transient episodes of expressive aphasia and ataxia. Three weeks prior to admission, she was admitted to another hospital with crushing substernal chest pain. Electrocardiogram and serum transaminase levels appeared to rule out an acute myocardial infarction and she was discharged. The next day she developed mid-epigastric pain, recurrence of aphasia and hemiparesis, and was admitted.

Examination revealed a blood pressure of 150/90 mmHg; pulse, 88/min; respiration, 14/min; and temperature 98°F. Scleral icterus, pallor, numerous petechiae, and ecchymoses were noted. The fundi were normal. The heart and lungs were normal. There was no lymphadenopathy or hepatosplenomegaly. The sensorium was clear, though the patient was globally aphasic and there was a right homonymous hemianopsia. There was a flaccid right hemiparesis and right hemihypesthesia which included the face. The plantar responses were both extensor. Hemoglobin was 8.3 g/100 ml; hematocrit, 24%; and WBC, 15,000/mm^3. The blood smear showed marked anisocytosis and poikilocytosis as well as helmet cells. Reticulocytes were 8.4%; platelet count, 26,000/mm^3; bilirubin, 0.8 (direct)/1.8 (total) mg/100 ml; and uric acid, 8.5 mg/100 ml. Coombs test, LE preparation, and serum proteins were normal. The EKG was normal. Cerebrospinal fluid examination showed 65 RBC/mm^3 and 3 WBC/mm^3; protein and sugar were normal. Bone mar-

[6] Case XIV: previously summarized by O'Leary and Tovell (148).

row examination revealed erythroid hyperplasia with many immature megakaryocytes. Urinalysis revealed 2+ protein and occasional white cells and red cells but no casts.

Despite large doses of intravenous hydrocortisone (200 mg/day) and of prednisolone (60 mg/day), blood transfusions, and antibiotics, she became oliguric and progressively more uremic (BUN, 23 mg/100 ml rising to 65 mg/100 ml) over the next eight days. She developed melena and on the ninth day expelled a dead fetus accompanied by considerable blood loss. She then became comatose and the right pupil dilated. She died on the eleventh day of the hospitalization.

Post mortem examination confirmed the diagnosis of TTP. There was a coronary artery thrombosis with a recent myocardial infarction of the right ventricle, left ventricle, and septum. Multiple fibrinous verrucae were present on the aortic and mitral valves. There were many areas of fresh and old encephalomalacia in the left frontal, parietal, and occipital lobes and the cerebellum. The typical hyaline thromboses of the blood vessels were found in all organs examined (Figures 1, 2). Review of the endometrial curettings did not reveal the characteristic arteriolar lesions. Histologic examination of the organs of the macerated fetus did not disclose the lesions of TTP.

Case XV. D.Z., a 43-year-old white male, was admitted to CPMC on September 2, 1962, with a 10-day history of headache. During that week, he complained of anorexia, nausea, abdominal pain, and dark urine. There was a transient period of aphasia. One year prior to admission, he underwent bilateral thoracic sympathectomy for Raynaud's phenomenon. Complete blood count, urinalysis, serum protein electrophoresis, sedimentation rate, skin and muscle biopsies, tests for cold agglutinins, LE preparations, and latex fixation were normal at that time. There was a trace of serum cryoglobulin. The admission physical showed a temperature of 101.4°F; pulse, 100/min; respiration, 30/min; and blood pressure, 140/85 mmHg. He was jaundiced and drowsy. There was no lymphadenopathy or hepatosplenomegaly. Thick, slurred speech, left facial weakness, and deviation of the tongue to the left were noted. Hemoglobin was 6.3 g/100 ml; hematocrit, 19%; WBC, 14,000/mm^3 with polys, 62%, bands, 22%, lymphs, 18%, and ESR, 45 mm/hr. Platelet count was 19,000/mm^3, and reticulocyte count, 19.3%. There were 15 normoblasts per 100 white cells. Bone marrow examination showed erythroid hyperplasia and a normal number of megakaryocytes without budding of platelets. Urinalysis showed 2+ glucose, negative protein, and 15–20 RBC/HPF. Tourniquet test was positive; prothrombin time, normal. The Coombs test was negative. Latex fixation and LE preparations were negative. Bilirubin was 4.5 mg/100 ml. Alkaline phosphatase, cephalin flocculation, and thymol turbidity were normal; FBS, 94 mg/100 ml; and BUN, 18 mg/100 ml. Fever persisted and neurologic symptoms progressed; he became unresponsive, obtunded, and developed a right hemiparesis. On the third day, he suddenly developed carpo-pedal spasm, a positive Chvostek sign, tetany, laryngospasm, and died. He had been treated with prednisone, 50 to 100 mg/day during the last 3 days of life.

Post mortem examination showed thrombosis of small systemic, splanchnic, and cerebral vessels. Small focal hemorrhagic infarcts occurred in the skin, mucosa of the gastrointestinal tract, kidneys, heart, adrenals, and the entire central nervous system except the spinal cord. There were prominent subendocardial hemorrhages; however, the valves were normal. Severe pulmonary edema together with severe pulmonary alveolar hemorrhage were noted. The microscopic lesions were characteristic of TTP.

Case XVI. J.E., a 28-year-old white female, was admitted to the CPMC on August 6, 1958, with the gradual onset over one month of spontaneous ecchymoses, hematuria, fatigue, malaise, anorexia, and jaundice. She was transferred from another institution where she had been given six units of blood because of severe anemia. Shortly before admission to CPMC, visual blurring, confusion, and delirium had developed. There was a history of exposure to a new hair dye three weeks prior to admission.

Examination revealed a blood pressure of 120/80 mmHg and temperature of 98.6°F. Jaundice, ecchymoses, and a left fundal, flame-shaped hemorrhage were present. Spleen, liver, and lymph nodes were not felt. Except for mental confusion, the neurologic examination was normal.

Hemoglobin was 11 g/100 ml; hematocrit, 36%; and WBC, 10,000/mm^3. Reticulocyte count was 14%. There was marked anisocytosis and poikilocytosis on the peripheral smear and 15 nucleated red cells per 100 white cells were seen. Platelet count was 25,000/mm^3. Osmotic fragility was normal. Bone marrow examination showed erythroid hyperplasia and numerous megakaryocytes. There was 2+ proteinuria and 5 RBC/HPF and 5 WBC/HPF. The serum protein electrophoretic pattern was normal. Tourniquet test was negative. Bleeding time, 14 minutes; VCT, 10 minutes; prothrombin time, 17 seconds. The Coombs test and serologic tests for syphilis were negative. LE preparations were negative. Bili-

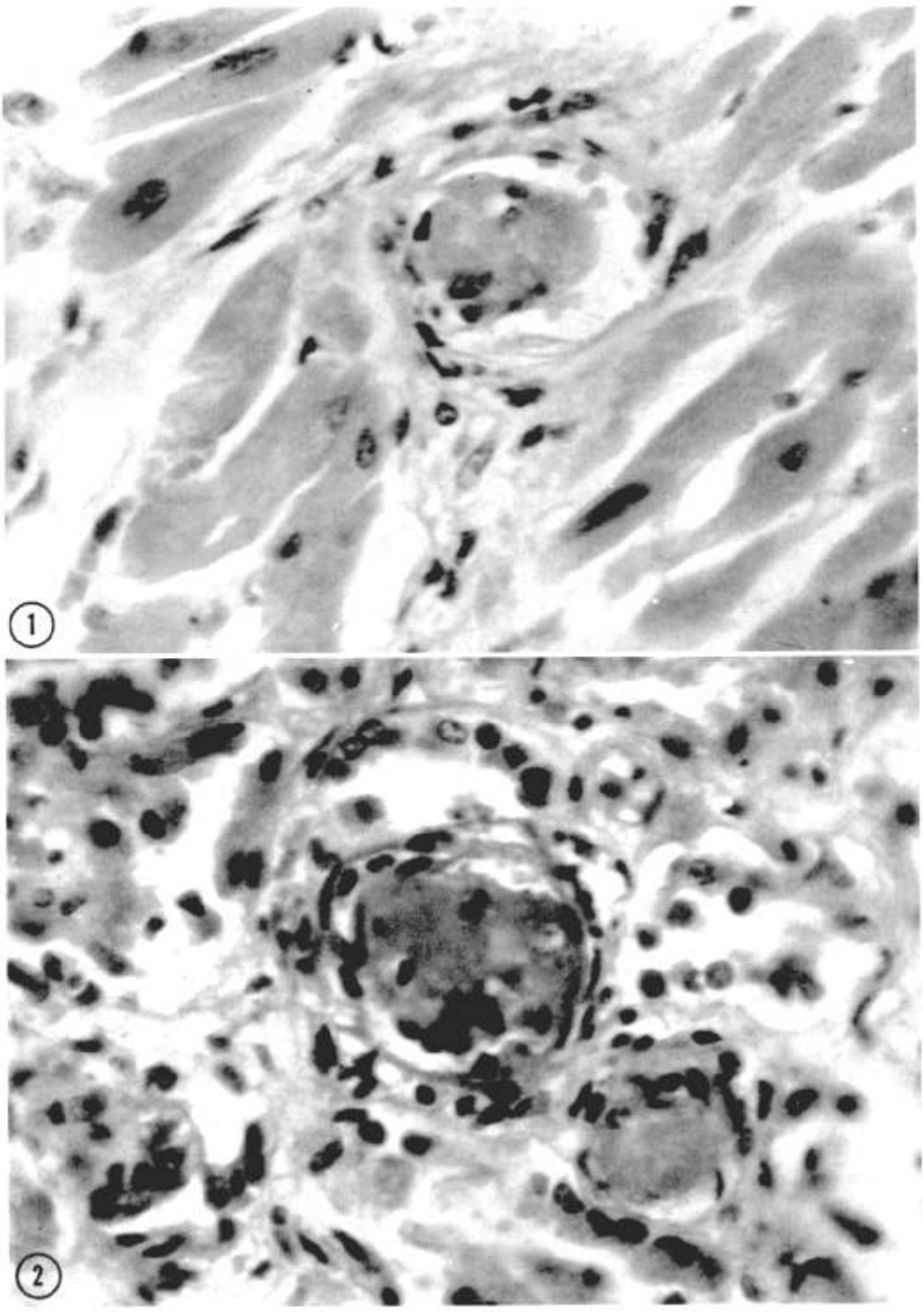

FIG. 1. Occlusion of arteriole in myocardium
FIG. 2. Occlusion of arterioles in kidney

rubin was 3.7 mg/100 ml; uric acid, 5.4 mg/100 ml; amylase, 56 units; and cephalin flocculation and thymol turbidity, negative.

She was treated with prednisone, 60 mg/day. There were periods of confusion and delirium during the hospitalization but no focal signs developed. Over the next few days, there was a steady improvement with a fall in white blood cell count and reticulocyte count, and the platelet count returned to normal. Steroids were gradually reduced and discontinued. She continues to do well and is hematologically normal seven years after her illness.

No pathologic confirmation of the diagnosis of TTP has been obtained in this case.

III. REVIEW AND DISCUSSION OF THE LITERATURE INCLUDING THE PRESENT CASES[7]

A. Incidence

There has been a sharp increase in the number of reported cases since 1950. Singer was able to review a total of 55 cases published before 1953 (185) and we have found an additional 216 cases up to June, 1964. This is probably due to greater recognition and reporting of cases although a true increase in the incidence of this disease cannot be ruled out. A retrospective analysis of 3,300 consecutive autopsies over 5½ years uncovered 3 cases of TTP (76).

B. Age and Sex

The age incidence has varied from infancy (5, 27, 44, 60, 78, 83, 92, 93, 101, 140, 182, 216) to 77 years (205); however, the majority of cases occurred between 10 and 39 years of age with the peak age incidence in the third decade. Females have been affected more frequently than males (3:2).

C. Clinical Picture

The majority of patients complain of vague non-specific symptoms before the development of the clear-cut syndrome. Some have considered this a prodromal phase of the illness (2, 8, 9). Since in most cases these symptoms are due to the basic disease, they will be considered as part of the present illness. As can be seen in Table II, the most frequently recorded chief complaints were due to neurologic abnormalities and hemorrhagic phenomena. Symptoms of anemia (fatigue, pallor, weakness) nausea, vomiting, and abdominal pain; fever; jaundice; and arthralgias and myalgias occurred less frequently.

[7] The present report encompasses cases cited in the literature up to June, 1964.

TABLE II

Chief Complaints of 246 Cases with TTP

	Cases	%
Neurologic	147	60
Purpura or hemorrhage	108	44
Malaise, fatigue, weakness	61	25
Nausea, vomiting	58	24
Fever	50	20
Pallor	43	17
Abdominal pain	26	11
Jaundice	23	9
Arthralgia or myalgia	16	7

TABLE III

Symptoms and Physical Findings of Patients with TTP

	Cases	%
Fever	237/243	98
Purpura, hemorrhage	241/251	96
Pallor or anemia	246/256	96
Neurologic	250/271	92
Proteinuria, hematuria, casts, or azotemia	191/217	88
Jaundice	113/271	42
Weakness, fatigue, malaise	92/271	34
Nausea, vomiting	69/271	25
Abdominal pain	36/271	13
Chest or other pain	21/271	8
Arthralgia or myalgia	18/271	7

Table III summarizes the symptoms and physical findings in the reported cases of TTP and indicates their frequency. The five outstanding and almost universal aspects of the disease will be considered first.

1) *Fever.*—Although fever or chills were noted in the history of only 82 cases, admission physical examination revealed fever in 133 patients. Eventually 237 of the 243 cases where temperature was reported were febrile. Fifty-four had temperatures between 102 and 105°F. In only six published case histories was fever specifically denied (10, 89, 119, 121, 194, and Case XVI). The cause of the fever is not known. It could be due to: 1) vascular involvement of the thermo-regulatory center in the hypothalmus (48), 2) tissue necrosis, 3) release

TABLE IV

Hemorrhagic Manifestations in 251 Patients with TTP

	Cases	%
Any hemorrhagic manifestation	241	96
Petechiae, purpura, ecchymoses	157	63
Retinal hemorrhages	47	19
Hematuria, gross	45	18
Epistaxis	29	12
Gingival hemorrhage	20	8
Melena	20	8
Menorrhagia	19	8
Hematemesis	16	6
Hemoptysis	4	2
Thrombocytopenia	216/224	96

TABLE V

Neurologic Manifestations of 271 Patients with TTP

	Cases	%
Any neurologic manifestation	250	92
Headache	92	34
Coma	84	31
Mental changes	70	26
Paresis	53	20
Seizure and coma	33	12
Aphasia	29	11
Syncope	25	9
Seizure	22	8
Visual changes	21	8
Dysarthria	18	7

of products of hemolysis (48), or 4) the release of endogenous pyrogenic substances from leukocytes (188) damaged as a result of antigen-antibody reaction. Fever, as a result of superimposed infection, is unlikely in view of the many reports of cases with negative cultures for bacterial organisms.

2) *Bleeding or Purpura.* (Tables III and IV)—Hemorrhagic manifestations were reported in 241 cases and specifically denied in a few (14, 35, 36, 43, 89, 93, 94, 114). Purpura and retinal hemorrhages were most frequent but major gastrointestinal (5, 13, 73, 98, and Case XIV) or genitourinary (1, 13, 17, 20, 50) hemorrhages were also seen. Thrombocytopenia was reported in all but 8 (14, 24, 36, 54, 89, 108, and Case IV) of the 224 cases in which platelets were estimated. Three of the patients with normal platelet counts had bleeding manifestations during the course of illness (54, 89, 108). The pathogenesis of the thrombocytopenia will be discussed subsequently.

3) *Anemia.*—Pallor was noted on physical examination in 116 cases and jaundice in 113 cases. Laboratory examination showed that anemia was an almost constant feature, being present in 244 of 256 cases. In only 10 cases was the hemoglobin greater than 11 g/100 ml (24, 36, 43, 51, 81, 136, 205, 212, 213, and Case VI). The anemia of TTP is discussed in greater detail in the section on laboratory tests.

4) *Neurologic Manifestations.*—Neurologic manifestations are summarized in Table V. Neurologic symptoms were elicited as part of the present illness in 190 of the 271 reported cases. Among these were headache and mental changes, including altered states of consciousness, agitation, confusion, and delirium. Paresis, aphasia, syncope, visual changes, dysarthria, seizures, coma, and other neurologic abnormalities, including cranial nerve palsies, paresthesiae, and vertigo were also reported. Subsequently, on examination, 75 of these patients were intact neurologically. This emphasizes the fact that neurologic abnormalities are remittent and subject to frequent, rapid change, so that, for example, hemiplegia or aphasia may clear completely a few hours after appearance (21, 42, 57, 64, 65, 71, and Case XIV). In some, the neurologic manifestations preceded by many months or years the recognition of TTP (21, 65, and Cases VI and XIV). One patient was initially hospitalized in a mental institution with acute catatonia before the true nature of her illness was discovered (87).

Eventually 250 patients had some neurologic abnormality. Whereas initially seizures or coma were present in only 30 patients, eventually one or both of these manifestations developed in 139 cases (51%) prior to death. Recurrent seizures accompanied by high fever and progression into coma constituted a frequent terminal event. In 21 cases no neurologic abnormalities were reported at any time during the illness (5, 12, 27, 53, 61, 67, 76, 83, 86, 92, 110, 140, 170, 181).

The frequency of the neurologic manifestations can be attributed to the common and striking involvement of small vessels of the gray matter of the hemispheres and the brain stem. Despite the widespread vascular occlusions there is often little cerebral infarction.

This may account for the transiency of the neurologic abnormalities. The neurologic manifestations and neuropathologic findings have been reviewed by a number of authors (1, 21, 96, 145, 217).

5) *Renal Disease.*—Involvement of the kidneys was manifested by significant proteinuria, hematuria, pyuria, and casts, or by azotemia, and was demonstrable in 191 of 217 cases in which these data were recorded (Table III). The blood urea nitrogen or non-protein nitrogen were significantly elevated in 66 of 139 cases. The clinical evidence of renal disease is not surprising in view of the frequent extensive involvement of renal blood vessels. Typical hyaline occlusions of capillaries and arterioles as well as a proliferative glomerulonephritis (12, 39, 42, 54, 82, 92, 105, 107, 112, 127, 128, 136, 141, 168, 182, 199) have been reported.

6) *Other Manifestations.*—Abdominal pain has not been stressed as a symptom. Thirty-six cases had abdominal pain as one of the presenting manifestations of the disease (1, 6, 11, 14, 19, 22, 29, 37, 43, 51, 54, 58, 62, 64, 67, 69, 73, 75, 94, 98, 101, 111, 128, 135, 144, 147, 151, 161, 166, 172, 182, 206, and Cases III and IX). In one case, acute abdominal pain with paralytic ileus led to an exploratory laparotomy (43). The abdominal pain has been attributed in some cases to pancreatitis secondary to thrombotic occlusion of pancreatic arterioles with pancreatic infarction (94). The serum amylase was elevated in 5 patients (14, 37, 51, 55, 94) and normal in 4 others (11, 54, 96, 105). In some cases the abdominal pain may be due to vascular occlusions in the wall of the gastrointestinal tract (43, 98). Diabetes, possibly as a result of pancreatic islet cell infarction, has been reported in 3 cases (14, 42, 55).

Hepatomegaly was seen in 25% of the cases and splenomegaly in approximately 20%. Slight lymphadenopathy has been mentioned in a few of the reports. Skin eruptions of various types have been reported in association with TTP (1, 27, 45, 53, 54, 58, 85, 107, 136, 170, 193, 194, 195).

Other manifestations of TTP have occurred infrequently. Among these have been Raynaud's phenomenon (36, 39, 80, 85, 169, and Case XV), malignant hypertension (55), extensive gangrene of the skin and subcutaneous tissues (123), periarteritis (13, 200), and agammaglobulinemia (78).

TABLE VI

Evidence of Hemolytic Anemia in Patients with TTP

	Cases	%
Anemia	246/256	96
Hb <5.4 g/100 ml..... 72		
Hb 5.5–10.4 g/100 ml.....174		
No anemia.....	10/256	4
Reticulocytosis 3.0–80.0% (avg. 19%)	148/164	90
Nucleated red blood cells (1–56/100 WBC)	93/?	
Coombs test positive.....	9/126	6
Jaundice.....	113/271	42
Bilirubin > 1.0 mg/100 ml (1.0–18.0)	143/163	88

The occurrence of TTP during pregnancy (39, 89, 135, 147, 164, 189, and Cases X, XII, XIII, and XIV) or in the puerperium (94) may be a chance occurrence. There may, however, be an etiologic relationship. In view of the reports of hemolytic anemia and thrombocytopenia in toxemia of pregnancy (158, 179) (*Vide infra*), this latter possibility deserves consideration. In three of the above ten pregnancies, a live birth resulted, and no abnormality was found in the child (39, 135, 189).; in the other seven there was either an abortion or a stillbirth.

D. Laboratory Findings

1) *Anemia.*—Anemia, frequently of severe degree, is a hallmark of this illness. As can be seen in Table VI, the hemoglobin level was below 5.4 g/100 ml in 72 and between 5.5 and 10.4 g/100 ml in 172. The average reticulocyte count was 19%; the highest, 80% (86). Nucleated red cells were frequently noted. Red blood cell indices were usually normochromic and normocytic. The most striking morphologic abnormality on peripheral blood smear was a bizarre distortion and fragmentation of the red cells (24) with the production of burr cells (178), irregularly contracted cells (59), and helmet cells (2). The significance of alterations in red cell morphology are discussed later. The Coombs test was rarely positive (10, 24, 42, 48, 83, 169, 214). Hyperbilirubinemia was noted in 143 of 163 cases in which bilirubin levels were reported. The indirect-reacting fraction was responsible for the elevation in almost all cases.

The morphologic abnormalities, together with the presence of nucleated red blood cells, reticulocytosis, and erythroid hyperplasia of the bone marrow, suggest that hemolysis is the major cause of the anemia of TTP. Red cell life span studies with Cr^{51}, performed in a small number of patients, support this concept (25, 72, 111, 127, 182, 193). It is not unlikely, however, that bleeding into the skin and gastrointestinal tract secondary to thrombocytopenia contributes significantly to anemia. In cross-transfusion experiments, normal blood given to a patient with TTP had a half-time survival of only 3 to 6 days (127, 193), suggesting either bleeding or an extrinsic hemolytic defect. Blood from a patient with TTP when transfused into a normal recipient had a shortened half-life of 15 days (193) suggesting that these red cells had been damaged sufficiently to cause their premature destruction or that an intrinsic red cell abnormality was present.

2) *Leukocytosis.*—Leukocytosis was seen in 145 of 239 cases; a leukemoid reaction was present in 32 of these with white blood cell count greater than 20,000/mm^3 (7, 9, 11, 25, 33, 42, 55, 57, 60, 69, 70, 71, 74, 76, 87, 88, 94, 121, 124, 131, 132, 140, 151, 170, 213, 216, and Cases III, VII, and XII). Leukopenia was seen in only 4 of 239 cases (11, 30, 81, 101). A marked "shift to the left," with the appearance of immature granulocyte precursors in the peripheral blood, was noted in 52 instances.

3) *Thrombocytopenia.* — Thrombocytopenia was an almost constant finding with platelet counts between 10,000 and 120,000/mm^3 in 216 of 224 cases in which platelets were estimated (Table IV). A normal platelet count may be observed at some time during the course of the illness, usually during a remittent phase making the significance of a single normal count in a case report difficult to evaluate. In 8 of the 271 cases, platelets were normal by direct count or by estimation (14, 24, 36, 54, 89, 108, and Case IV). Examination of bone marrow aspirations usually reveals a normal or increased number of immature megakaryocytes with smooth borders. Whether this represents decreased formation of platelets or increased peripheral utilization has not been determined. Platelet life span studies would be difficult to interpret in bleeding or previously transfused patients. Platelet antibodies or agglutinins have been seen in only 3 (3, 88, 157) of 16 (17, 25, 30, 47, 62, 65, 105, 111, 116, 119, 131, 172, 195) tested cases. The tourniquet test is usually positive. Other coagulation studies reveal normal to moderately prolonged bleeding time and clotting time and, usually, a poor clot retraction. Prothrombin time may be prolonged (2, 11, 15, 30, 33, 54, 57, 63, 75, 88, 91, 99, 115, 116, 120, 124, 171, 176, 205, Cases IV, VII, and XVI) or normal (26, 29, 31, 36, 41, 51, 64, 68, 85, 106, 110, 111, 112, 117, 120, 134, 135, 169, 177, 182, 184, 187, 195, 203, 206, 212, 214, 215, Cases VIII, IX, XIII, and XV). Hypofibrinogenemia has been reported in 3 cases (30, 63, Case XII), suggesting the possibility of fibrinogen consumption by intravascular thrombosis. The incomplete prothrombin consumption noted in some cases (2, 30, 31, 44, 51, 64, 71, 99, 116, 140, 176, 184, 212) is probably due to the thrombocytopenia.

4) *Serum proteins and serologic tests.*—Usually no or only minor non-specific abnormalities of the serum proteins have been found. In 3 cases agammaglobulinemia was reported (78). The serologic test for syphilis was positive in 9 of 73 cases tested (33, 46, 49, 57, 80, 86, 115, 205, and Case XII). Five of these may have been "biologically false positive tests" (33, 57, 80, 86, 115). No abnormalities in other serologic tests could be found consistently enough to give them any significance.

5) *Electroencephalogram.*—The electroencephalogram (EEG) may be normal, may indicate a diffuse bilateral cortical abnormality (31, 187), or may suggest a specific focal lesion (21, 31, 90, 105). The cerebrospinal fluid often shows a slight increase in pressure and protein. Pleocytosis is uncommon (98, 120, 128, 181) and subarachnoid hemorrhage is seen infrequently (111, 195).

6) *Electrocardiogram.* — The electrocardiogram may be normal or show non-specific ST-T wave abnormalities. An acute, grossly visible, myocardial infarction has been found at postmortem examination without electrocardiographic evidence of it prior to death (143, 177, Case XIV).

7) *Biopsy results and pathology.*—The pathologic diagnosis has been made during life by skin and muscle biopsy in only 6 of 27 attempts (12, 45, 65, 176, 198, 212), by lymph node biopsy (4) in 4 of 5 attempts (138, 170, 181, 195), by paraffin section of bone marrow particles in 8 of 17 attempts (57, 138, 174, 216),

and by examination of a surgically removed spleen in 16 cases in which splenectomy was accomplished without immediate operative mortality (2, 25, 39, 64, 79, 90, 99, 105, 132, 154, 155, 171, 180, 184, 193). Occasionally reexamination of surgically removed organs [e.g., appendix (136, 195), breast (33), endometrial curettings (197)] may confirm a diagnosis of TTP when the progressive clinical picture prompts review of such slides.

At post mortem examination, the characteristic occlusions may be found in any organ but are seen most frequently in the heart, brain, kidneys, pancreas, and adrenals. There is a striking absence of inflammatory change in the involved vessels and a rather limited area of infarction considering the number of vessels involved. This may be due to incomplete occlusion of the involved vessels (16, 35). Although these widespread vascular changes are considered diagnostic, many authors, including Moschcowitz, have pointed out that lesions resembling TTP may occur in a number of other conditions, such as burns (139), mercury poisoning (139), leukemia (102, 167), malignant tumors (109), rickettsial diseases (75), and others (103, 153).

The pathologic lesions were originally described by Baehr et al (9) as occlusions of arterioles and capillaries by an amorphous, hyaline-like material accompanied by endothelial proliferation. Gore (89) demonstrated subintimal depositions of a hyaline-like material in the vessel wall, the so-called "prethrombotic lesion." This occasionally occurred at points in the vessel wall having no demonstrable occlusion. Gore postulated that this resulted in damage to the overlying endothelium with resultant local platelet agglutination, thrombosis, and endothelial proliferation. Orbison (149, 150), employing serial sections and three-dimensional models, demonstrated aneurysmal dilatation of vessels at the arteriolar-capillary junction. However, there is still a question as to whether the so-called "prethrombotic lesion" truly represents a primary vascular damage or is the result of a reendothelialized, intravascular thrombosis. Endothelial proliferation could also be a response to intravascular thrombosis (142).

The nature of the occluding material is still in doubt. Originally it was thought to represent agglutinated red cells (139) or platelets (9). The lack of stains specific for platelets made a direct proof of this impossible and this conclusion was reached by exclusion when the material failed to stain for hemoglobin or fibrin. Craig and Gitlin (58) in 1957, employing immunofluorescent techniques, demonstrated that the material stained for fibrin. Komori (109), using similar techniques in 1962, found both platelet and fibrin material. Electron microscopic studies of the vascular lesions of TTP have not been reported but would be very helpful in determining the true nature of the occluding hyaline material.

IV. ETIOLOGY AND PATHOGENESIS

A number of theories have been proposed to explain the nature and cause of this complex disorder. Its etiology or etiologies, however, remain unknown and its pathogenesis is only incompletely understood and not conclusively proven. Among the causes which have been implicated in the etiology and pathogenesis of TTP, the following will be considered: 1) toxins, 2) drug sensitivity, 3) bacterial infections, 4) autoimmune reactions, 5) collagen disease and related disorders, 6) abnormalities of serum lipids, 7) intravascular thrombosis, and 8) hemolysis as related to intravascular thrombosis.

Initially, TTP was thought to be due to a toxin capable of causing hemolysis and platelet agglutination with the production of vascular occlusions secondary to platelet thrombi (71, 75, 139). However, toxins have not been implicated with certainty in any reported case.

At various times it was postulated that drug allergy plays an important role in the development of TTP (196, 198). Patients with TTP are often treated with a variety of agents (including aspirin, phenacetin, antibiotics, and antihistamines) during the early phases of their illness before the true nature of the disease becomes apparent. It is probable that the disorder had been initiated prior to any drug treatment. In a few cases, however, the possibility that a drug did play an etiologic role seemed somewhat more likely since the drug was given for an unrelated illness prior to the development of symptoms or signs of TTP. Such reports have included cases in which sulfa drugs (17, 31, 53, 121, 136, 195, 213), penicillin (17, 143, 213), iodine (67), oxophenarsine (196), procaine and chlorpropamide (198) have been administered prior to the appearance of TTP.

Bacterial infection as a cause of TTP is unlikely in view of the many reports of negative cultures for bacterial pathogens. Viruses have been suggested by some (133, 137) as etiologic

agents, but conclusive proof of this hypothesis is lacking.

It has been suggested that TTP is an autoimmune disorder, but there is not much evidence to support this concept. The rarity of demonstrable antibodies against platelets and red cells has already been mentioned. In addition, transfusion of plasma from a patient with this disease to a normal volunteer caused no untoward effects (25), indicating absence of circulating antibody against red cells or platelets.

There has been considerable speculation regarding the possibility that TTP is primarily a vascular disease (89, 150), an allergic disorder (192, 196, 198), or a collagen disease (11, 12, 13, 107, 113, 117, 168, 184, 200, 201). The previously discussed studies of Gore and Orbison (89, 150) demonstrated definite vascular lesions, but, as mentioned, these changes could be secondary to intravascular thrombosis. There are some cases, clinically indistinguishable from the usual case of TTP, which at post mortem examination disclose vascular lesions of both TTP and polyarteritis (13, 200). Such cases are distinctly rare, however. The usual histologic finding in TTP is a vascular occlusion with little or no cellular infiltration. There are a few case reports of patients with past histories of acute rheumatic fever (1, 11, 75, 86, 168, 169), rheumatoid arthritis (12, 17, 20, 38), rheumatoid spondylitis (138), discoid lupus (132), and a variety of minor allergic manifestations. Eosinophilia has been noted rarely (74).

Some have attempted to draw a parallel between TTP and systemic lupus erythematosus (SLE) (12, 107, 113, 117, 168). Although a syndrome clinically indistinguishable from TTP may occur during the course of SLE (42, 111, 184), the two diseases differ significantly in sex incidence, duration, course, complications, prognosis, response to therapy, and pathology. In the reported 271 cases, there are 64 patients in whom LE preparations were done. Only 7 of these were positive (39, 42, 111, 113, 117, 184, 201); one of these (111) was not proven TTP on pathologic examination and probably represented systemic lupus erythematosus masquerading as TTP. If the histologic changes of "wire loop" kidney lesions, "onion-skin" splenic arterioles, or Libman-Sachs endocarditis are used as criteria for the diagnosis of SLE, only 13 autopsied cases (11, 12, 36, 42, 107, 113, 117, 168, 199, 200, 201, 206) which were reported as TTP could also be diagnosed as SLE. Verrucous endocarditis was found in 28 other cases (9, 11, 21, 40, 49, 63, 69, 76, 80, 85, 86, 110, 123, 132, 136, 157, 189, 195, and Cases I, IV, VI, VII, X, XI, XIII, XIV) of the 237 autopsied cases of TTP but the histology of these verrucae varies considerably from that of Libman-Sachs endocarditis. In TTP the verrucous lesions are relatively acellular thrombotic vegetations, whereas in SLE fibrinoid necrosis and inflammatory reaction are prominent (9, 63, 69, 80). The thrombotic vegetations of TTP were seen more commonly in the patients with prolonged illness. The average survival of those cases with the lesion was ten months or three times longer than the over-all survival of patients with TTP.

A syndrome characterized by anorexia, wasting, and jaundice with anemia and thrombocytopenia has been produced in rats fed a choline-rich, high-fat diet (165). Histologic examination of tissues from many organs of these animals revealed vascular lesions similar to those of TTP. What relation, if any, these findings have to the human disease is not known. There have been no reports of abnormal blood lipids in patients with thrombotic thrombocytopenic purpura.

The histologic changes of TTP, which have already been described, are compatible with the assumption that intravascular thrombosis is a pathogenic feature of this disease. The reports of hypofibrinogenemia and hypoprothrombinemia and the favorable response to heparin therapy of several patients with TTP (17, 160) support the concept that the clinical manifestations are due to widespread intravascular thrombosis. Various hypotheses have been advanced to account for the thrombosis including a deficiency of normal antithrombin (16, 35), an excess of antihemophilic globulin or prothrombin activator (16, 89), and the development of increased platelet adhesiveness with the release of platelet thromboplastin (35). Another suggested possibility is that TTP represents a clinical example of the experimentally produced, generalized Shwartzman reaction (9, 204). In this model, bilateral renal cortical necrosis and widespread vascular occlusions are produced in rabbits after two appropriately spaced injections of bacterial endotoxin (183, 207, 208). The reaction resembles TTP in some of its histologic characteristics (27) and the resulting thrombocytopenia (125) and hypofibrinogenemia (207). It is thought to result from the development of a hypercoagulable state with widespread intravascular thrombosis, especially in the renal glomeruli with resultant bilateral cortical necrosis. The fact that the reaction can be prevented by treatment with heparin (207), the occasional report of TTP developing shortly after immunization (78), and the report of a syndrome indistinguishable from TTP during meningococcemia (144) lend support to this hypothesis. Thrombocytopenia, according to this theory, would be the result of platelet consumption during coagulation. The effect of the generalized Schwartzman reaction on red cells has not been studied although a mild hemolytic anemia has been documented in rabbits given repeated injections

TABLE VII

Differential Diagnosis of TTP

	Hemolytic anemia	Coombs test	Thrombopenia	Leukopenia	CNS manifest.	Fever	Renal disease
					transitory		
TTP	+++	±	++++	0	++++	++++	++++
Idiopathic thrombocytopenic purpura	+	0	++++	0	+	0	0
Idiopathic autoimmune hemolytic anemia	++++	++++	+	0	0	0	0
Symptomatic hemolytic anemia	+++	++	+++	++	+	++	+
Evans syndrome	++	++	++++	0	0	0	0
SLE	+++	++	++	+++	++	++	++

of bacterial endotoxin (100). This hemolysis, however, was thought to be due to reticulo-endothelial hyperplasia with increased random destruction of red cells and was not similar in severity or red cell morphology to the hemolysis seen in TTP.

The possibility that the red cell damage in TTP was due to mechanical trauma was suggested by Monroe and Strauss in 1953 (136). Brain et al (24) recently called attention to the bizarre red cell morphology seen in TTP and reviewed the literature (2, 5, 136, 182). On peripheral blood smear, fragmented triangular, helmet-shaped or "burred" erythrocytes are seen. Similar red cell changes may be seen in eclampsia (158, 179), bilateral renal cortical necrosis (5, 83) malignant hypertension (5), acute glomerulonephritis (5), after the placement of teflon prostheses during cardiovascular surgery if these are not endothelialized (175), and in other conditions characterized by interruption of the integrity of the normally smooth vascular endothelium. A roughened endothelium, either due to a primary vascular disease or to the intravascular deposition of fibrin, would then lead to red cell damage, morphologic distortion, and premature removal from the circulation. Such red cell changes, hemolysis, hypofibrinogenemia, and fibrin deposition in renal glomeruli have recently been demonstrated in rabbits after thrombin infusion (23). Since products of hemolysis may produce a hypercoagulable state (160), a vicious cycle may be established.

Although some of these theories offer much to recommend their acceptance as fact, it should be re-emphasized that further evidence must be presented before any can be thought proven.

V. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of TTP includes idiopathic thrombocytopenic purpura, idiopathic autoimmune hemolytic anemia (IAIHA), symptomatic hemolytic anemia, the Evans syndrome (co-existence of immune hemolytic anemia and thrombocytopenia), systemic lupus erythematosus (SLE), periarteritis nodosa, eclampsia, drug reaction, toxin exposure, sepsis, aplastic anemia, paroxysmal nocturnal hemoglobinuria, and leukemia. From Table VII, it can be seen that transitory, but marked neurologic abnormalities, hemolysis with a negative Coombs test, evidence of renal disease, and fever set TTP apart from the other diseases.

A syndrome of hemolytic anemia with "burr cells" and "helmet cells" and thrombocytopenia has been described in association with eclampsia (158, 179). At autopsy, renal cortical necrosis may be found but the widespread arteriolar lesions characteristic of TTP are not found. The presence of pregnancy, hypertension, and severe azotemia may help in the clinical differentiation from TTP. The decision may be difficult since TTP has been described during or shortly after pregnancy in 11 cases, as previously mentioned.

TTP has been described in children (2, 9, 24, 27, 34, 45, 58, 76, 78, 101, 105, 141, 143, 170). There have been 7 cases under one year (5, 27, 44, 78, 83, 101, 216), 21 cases between 1 and 10 years (9, 24, 34, 45, 58, 62, 64, 70, 76, 78, 101, 119, 170, 182, 193, 199, 216), and 11 cases between 11 and 14 years (2, 15, 22, 105, 127, 141, 143, 173, 186, 201, 215). In these cases, the typical arteriolar lesions were found in many organs at autopsy or in a surgically removed spleen (64) or lymph node biopsy (170). Some of these cases had evidence of severe renal failure (5, 15, 22, 24, 44, 62, 64, 70, 83, 119, 127, 182, 199, 216) and were clinically indistin-

TABLE VIII

Duration of Illness in 238 Patients with TTP

Duration (days)	Number patients	Days	
		Prior to admission	In hospital
<90	189	16 (1–62)	14 (1–70)
91–365	34	120 (2–210)	52 (6–300)
>365	15	798 (1–16 yr.)	427 (6 days to 12 yr.)

guishable from the so-called "hemolytic uremic syndrome" first described by Gasser et al (83) in which either bilateral cortical necrosis (61, 83) or the arteriolar lesions of TTP were found exclusively in the kidneys (5, 30, 61, 92, 93). As the name implies, hemolytic anemia with distortion of red cells is a feature of the illness but thrombocytopenic purpura is also frequently seen. The syndrome usually follows a febrile illness, frequently characterized by diarrhea, dehydration, and prostration. If the renal failure can be reversed, the children often recover and a histologic diagnosis may not be obtained (5, 60, 61, 121, 140, 182). Since the clinical picture, the pathologic findings in some cases, and possibly the pathogenesis are similar to TTP in the adult, all of these cases have been included in the present review. McQuiggan et al (126) and O'Connell et al (146) have recently reviewed the cases of Gasser's syndrome and pointed out that all occurred in children under ten years of age.

VI. PROGNOSIS AND THERAPY

Thrombotic thrombocytopenic purpura usually runs a rapidly progressive and fatal course and the majority of patients die within three months of onset of the disease (Table VIII). It is not possible, however, to predict with certainty the outcome or duration of illness in an individual case due to the occasional more chronic form of the disease (33). It should be noted that frequently patients with a long illness prior to hospitalization died shortly after admission and others with severe neurologic or hemorrhagic manifestations on admission lived many months or years after the presenting symptoms and signs.

Twenty-seven patients included in this review were still alive at the time of reporting. Ten of these cases, however, represent examples of the hemolytic-uremic syndrome in which the prognosis appears to be different from classical TTP (5, 60, 61, 92, 121, 140, 182); one case was apparently due to meningococcemia which cleared with control of the infection (144); and two cases represent examples of systemic lupus erythematosus (111, 184) presenting as thrombotic thrombocytopenic purpura. Thus, only thirteen reported cases of classic TTP were still alive and apparently cured at the time of reporting (17, 30, 31, 64, 99, 154, 170, 171, 173, 180, and Case XVI). Four of these cases did not have histologic proof of the diagnosis (17, 31, 173, Case XVI). The age and sex incidence in this small group corresponded to that of the entire group. Therapy in these cases has varied. In addition to blood transfusion, one case was treated with heparin and adrenocortical steroids (17); four cases with large doses of steroids alone (30, 31, 170, Case XVI); two cases with testosterone and adrenal steroids (31, 173); one case with exchange transfusion (173); and six cases with adrenal steroids combined with splenectomy (64, 99, 154, 171, 180).

Some have proposed that large doses of adrenocortical steroids, alone (31) or combined with splenectomy (99, 204), are effective in the management of this disease. Forty-six cases have been treated with daily doses of at least 40 mg of prednisone or 300 mg of cortisone (18, 25, 26, 30, 31, 39, 40, 42, 47, 48, 52, 57, 72, 82, 88, 99, 105, 106, 111, 116, 121, 123, 138, 152, 154, 155, 169, 172, 173, 176, 180, 184, 193, 195, 202, 206, Cases VIII, XII, XIII, XIV, XV, XVI). Only nine of these cases were still alive at the time of reporting. Many others have been treated with lower doses of steroids or ACTH without effect. It does not appear that the disease is appreciably altered by this form of therapy in most cases.

Splenectomy has been performed in 33 cases (2, 5, 25, 26, 32, 39, 46, 52, 64, 69, 72, 79, 80, 90, 99, 105, 132, 154, 155, 168, 169, 171, 180, 182, 184, 193, 201, 203, 206). The effectiveness of only 23 can be evaluated since the others were preterminal at time of operation. One was followed by a two year remission (132), one, by a nine month remission (79), and six others were alive at the time of reporting (64, 99, 154, 171, 180).

Other forms of therapy which have been attempted without success include exchange transfusion (65, 83, 101, 216), Imuran® (39),

nitrogen mustard (52, 193), streptokinase (48), and diethylstilbestrol or testosterone (50).

Therapy with fibrinolytic agents has not been given an adequate trial. In view of the possibility that the disease is due to intravascular thrombosis, it is conceivable that these agents could have a place in the treatment of this disease (56). Their usefulness, however, would depend on the presence of an intact plasminogen system capable of being activated. This might not be the case if a recent burst of in vivo fibrinolytic activity had occurred (48) in response to widespread intravascular thrombosis. The hazard of bleeding from thrombocytopenia in these patients has caused most physicians to hesitate before starting therapy with heparin. In view of the report of a favorable response to this therapy in one case (17) and the possibility that the disease is due to intravascular thrombosis, treatment with this agent under carefully controlled circumstances may eventually prove to be an effective form of therapy.

VII. SUMMARY

The clinical and laboratory manifestations of thrombotic thrombocytopenic purpura (TTP) were reviewed in the 16 cases seen at the Columbia-Presbyterian Medical Center and in the 255 patients reported in the literature. Fever, hemolytic anemia, purpura or other bleeding, transient or permanent neurologic signs, and renal disease are the hallmarks of TTP.

Severe anemia was accompanied by changes in red cell morphology, consisting of fragmentation, burr cells, and helmet cells. Nucleated red blood cells were seen frequently. Thrombocytopenia occurred in 96% of the cases. Leukocytosis with a marked shift to the left was frequently present and a leukemoid reaction occurred in some cases. The diagnosis appears most readily confirmed by biopsy of bone marrow, lymph nodes, or by splenectomy. At post-mortem examination, the heart, kidneys, adrenals, pancreas, and brain were most frequently involved. Microscopic examination showed occlusion of arterioles and capillaries by an homogeneous eosinophilic material without inflammatory reaction. The etiology and pathogenesis of this syndrome are not known. Although variable in course, the disease was usually rapidly progressive with 72% of cases dying within 90 days. No evidence of consistently effective therapy was found; however, the role of corticosteroids, splenectomy, and of heparin in treatment are reviewed.

ACKNOWLEDGMENTS

The authors are grateful to Drs. H. Heinemann, E. Hirschberg, A. Manska, G. Nicolis, and G. Smarth, and to Mrs. C. Gordon for translations. Mrs. B. Hatherley, Mrs. F. Lefcourt, Mrs. J. Reibman, and Miss B. Rotter rendered valuable secretarial assistance.

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