0025-7974/81/6006-0413$02.00/0
MEDICINE

Vol. 60, No. 6
Printed in U.S.A.

Thrombotic Thrombocytopenic Purpura

REPORT OF 25 CASES AND REVIEW OF THE LITERATURE

REN L. RIDOLFI, M.D. AND WILLIAM R. BELL, M.D.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is an unusual syndrome characterized by the clinical picture of microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic symptoms, renal disease, and fever (6, 10, 149).

Amorosi and Ultmann reviewed 271 cases reported in the medical literature from the time of initial description in 1925 by Moschcowitz to mid-1964 (6). The present paper reviews 250 cases reported in the English medical literature from 1964 to the present (1980) and 25 cases diagnosed at the Johns Hopkins Hospital from 1930 to the present (1-5, 8, 9, 12-17, 19-22, 24-28, 30, 33, 34, 36-43, 45-51, 53-70, 72-74, 77-79, 81-89, 91-95, 98-101, 103, 105, 107-118, 120, 122-124, 127, 130-138, 141-148, 150-155, 160-162, 164, 167, 170-188, 193-207).

Historical Perspective

In 1925 Eli Moschcowitz first reported a case of what is now generally referred to as thrombotic thrombocytopenic purpura (125). He described a fulminant febrile illness in a 16-year-old female with hemolytic anemia, bleeding, renal failure, neurologic symptoms, and widespread small vessel hyaline thromboses. The etiology of the process was not apparent but it was felt that agglutinated or congealed red blood cells comprised the vascular occlusive lesions.

Baehr, Klemperer, and Schifrin published a series of similar cases in 1936, by which time thrombocytopenia was recognized as a contributing factor to the bleeding problems in these patients (11).

Occlusive platelet thromboses were felt by these authors to be the important pathologic alteration. Others including Gore (75), Orbison (139), and Singer (180) observed underlying pathologic changes within the involved vessels, so-called prethrombotic lesions and microaneurysms, and the beginning of a continuing controversy regarding the precise pathology of TTP began (71). TTP led to death in virtually all early described cases, the clinical course ranging from hours to several weeks in duration. Among the first 116 cases described only 4 patients survived (35).

The hemolysis was first suggested by Monroe and Strauss to result from mechanical trauma to red blood cells (121). Inclusion of TTP among the various microangiopathic hemolytic anemias is now uniformly agreed upon (23), and is a requisite feature for diagnosis.

The original triad of hemolytic anemia, thrombocytopenic purpura, and neurologic disease was expanded to include fever and renal disease by Lukes et al in 1961 (104), and further emphasized by Amorosi and Ultmann in 1966 (6).

Therapeutic efforts including corticosteroids (28, 58), heparin (18, 161), antiplatelet agents (5, 7, 63), splenectomy (17, 53, 160, 170), exchange transfusions (26, 126, 150, 186), plasma infusion (32, 33), and others have been associated with varying and generally unpredictable success. Burke and Hartmann in 1959 described long term survival in two patients with TTP following therapy with large doses of steroids (29). In the same year the first report of remission in TTP following fresh blood transfusion was documented (168).

The spectrum of the syndrome broadened when it became apparent that patients with TTP could pursue a more protracted clinical course. This type of case was the exception rather than the rule, and in the review of Amorosi and Ultmann in 1966, only 13 patients with classic TTP survived among 271 reported (6).

Summary of Cases Diagnosed at Johns Hopkins Hospital

Twenty-five cases of TTP have been diagnosed since 1930 at The Johns Hopkins Hospital. Four have been previously reported (117). A single case

From the Departments of Medicine and Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Dr. Bell is supported in part by Research Grant HL01601-33 from NHLBI of the National Institute of Health, The Whitehall Foundation and is a Hubert E. and Anne E. Rogers Scholar in Academic Medicine. Dr. Ridolfi is currently with the Southern California Kaiser Permanente Medical Group.

occurred in 1932 and was diagnosed retrospectively on the basis of clinical and autopsy findings; a single case was diagnosed at autopsy during the 1940s, and four cases were diagnosed with autopsy confirmation during the 1950's. Prior to 1965 all patients with TTP died of their disease and the diagnosis was confirmed by autopsy. Subsequent to 1965 15 patients with TTP were seen, 6 of whom survived the disease.

Twenty-two of 25 patients exhibited the triad of microangiopathic hemolytic anemia, thrombocytopenic purpura, and neurologic symptoms. Two of three patients not demonstrating the classic triad were autopsied and showed findings typical of TTP, while the third had thrombocytopenia, neurologic symptoms, renal disease, and fever, but only mild anemia. Autopsy findings were consistent with TTP.

Fourteen of 25 patients exhibited the complete pentad of clinical features; 20/25 manifesting a fever of greater than 99.6°F during their clinical course and 18/25 displaying some evidence of renal disease. Only 4 of 25 patients developed frank renal failure.

The mean age of these 25 patients was 40.5 years with a range of 19–77 years. Seventeen were female and 8 male. Fifteen were Caucasian and ten were black. The most common chief complaint was weakness, followed by headache, dizziness, confusion and dysarthria. Twenty-two had fever (>101°F oral). Hemorrhage was observed in all patients. In 21 it was manifest cutaneously, 9 experienced gross hematuria and 4 had retinal bleeding. Confusion was the most common finding on neurologic examination (19 patients). A total of 14 had paresis, 10 headache, and 8 had aphasia.

The mean hematocrit value for these 25 patients at time of presentation was 21.3% (SE ± 1.4) with a range of 10–42%. The mean white blood count was 14,300/mm^3 (SE ± 1.6) with a range from 3,000–40,000/mm^3. All patients with one exception were severely thrombocytopenic with the mean platelet count being 20,500/mm^3 (SE ± 4,000) with a range from 1,900 to 70,000/mm^3. The reticulocyte count mean value for the group was 14% (SE ± 2%) with the range from 1.6 to 44%. The plasma fibrinogen concentration mean value was 225 mg/dl (SE ± 18) with the range from 77 to 385 mg/dl. The prothrombin time was within the normal range in all but three patients, while the partial thromboplastin time was abnormal in only one patient. Fibrinogen-fibrin degradation products (FDP-fdp) were measured in eight patients and found to be elevated above normal in 6. An elevated SUN was found in 19 patients and the serum creatinine was elevated in all 19. One patient was anuric on presentation. The total bilirubin mean value was 4.5 mg/dl (SE ± 1.0) with the range from 0.5 to 22 mg/dl. In these patients the direct reacting bilirubin was 3.5 mg/dl (SE ± 1.4) with the range from 0.6 to 15.0 mg/dl. The Coombs test was negative in all patients. No patient evidenced LE cells and the ANA titer was elevated in two patients. The urine analysis was abnormal in 23 patients, with detectable proteinuria in 22, red blood cells (gross and microscopic) in 17 patients, excess white blood cells in 5 patients and granular casts in 2 patients.

Four of our cases are described in detail, each of which exemplifies important aspects of the TTP syndrome.

Case Presentations

Case 1

P.F. was a 77-year-old white female admitted for evaluation of pancytopenia. Her present illness began three weeks prior to admission when she was given sulfonamides (Gantrisin) for a urinary tract infection. She became febrile the day the medication was started and noted chills, abdominal pain, nausea and vomiting over the next 5 days. After 7 days sulfonamides were discontinued and Tetracycline was begun. The patient noted continued fatigue and mild confusion. Five days prior to admission her hematocrit value was 14.9%, white blood cell count 5,500 mm^3 and platelet count 23,000 mm^3 (hematologic values obtained 1 month previously had been entirely normal). She received one unit of whole blood and a unit of packed red blood cells, but her hematologic picture failed to improve. One day prior to transfer, the patient experienced an episode of dysphasia associated with numbness and weakness of the left hand which lasted approximately 5 minutes.

On admission to Johns Hopkins Hospital physical examination revealed a confused and anxious normally-developed female. Blood pressure was 150/70 mm Hg, pulse 85/min, and respiration 18/min. Examination of the extremities revealed small petechiae over the inner aspect of the thighs bilaterally. Retinal hemorrhages were present in the left fundus. Initial laboratory studies showed a hematocrit value of 20%, white blood cell count of 9,800 mm^3, platelet count of 20,000 mm^3, reticulocyte count 7.0%, bilirubin of 3.9 mg/dl, SGOT greater than 700 u/liter (normal 0–19 u/liter), alkaline phosphatase 112 u/liter (normal 10–32 u/liter), and normal blood calcium, glucose, amylase, and electrolytes. A peripheral smear demonstrated numerous fragmented red blood cells, many polychromatophilic red cells, occasional nucleated red cells, and markedly diminished platelets. Urinalysis demonstrated mild proteinuria, many white blood cells, and no red blood cells.

Several hours after admission she experienced an episode of aphasia. A tentative diagnosis of TTP was made and the patient begun on methylprednisolone 65 mg IV followed by 50 mg q 12 hour. Ampicillin was administered for a presumed urinary tract infection.

Other laboratory findings included a haptoglobin of 16 mg/dl, weakly positive antinuclear antibody (ANA), fibrinogen of 320 mg/dl, and negative FDP-fdp. A urine culture grew significant numbers of *E. coli* and a bone marrow aspirate revealed a hypercellular marrow with pronounced erythroid hyperplasia. A Coombs test was negative.

On the fourth hospital day the hematocrit was 20.8%, reticulocyte count 21.0%, and platelet count 112,000 mm^3. She was given two units of packed red blood cells and was continued on steroids.

The patient's hematologic problem improved gradually and on the 21st hospital day, prior to discharge, her hematocrit value was 36%, platelet count 200,000 mm^3, and peripheral smear normal.

Following discharge steroids were tapered over a several month period and she remains well 2.5 years later.

Comment: This patient displayed a microangiopathic hemolytic anemia, thrombocytopenia, transient neurologic symptoms, and possible renal disease consistent with TTP. The onset of her illness was temporally related to sulfonamide therapy for a lower urinary tract infection. Additional history revealed she had experienced a febrile illness approximately 1 year previously while receiving sulfonamides (Gantrisin) for another urinary infection. TTP in this instance most likely was a drug-related hypersensitivity-type process. This has been reported on rare occasions previously (1, 22, 40, 81, 137, 140, 148).

Case 2

B.L. was a 45-year-old black female with known hypertension and two previous cerebrovascular accidents, one 10 years before admission and the second 1 month before admission, associated with no significant residual deficit.

She presented to the Johns Hopkins Hospital with a one-day complaint of right sided weakness followed by progressive disorientation. On the day of admission she developed nausea, vomiting, and hematochezia. Physical examination revealed a blood pressure of 160/85, temperature 99°F, pulse 90, and respirations 18 per minute. She had decreased motor strength of the left upper and lower extremities. No other significant findings were noted. Her medications included quinidine, Reserpine, Hygroton, and KCl. Her hematocrit value was 19%, white blood cell count 14,300 mm^3, and platelet count 8,000 mm^3. A peripheral blood smear revealed poikilocytosis with many fragmented cells. A reticulocyte count was 11.2%. PT, PTT, and fibrinogen were normal. FDP-fdp were mildly positive at titer of 1:16 and on repeat of 1:32. Direct Coombs, circulating anticoagulants, and an in vitro clot retraction inhibition test performed using normal platelets, quinidine, and patient plasma were normal. A bone marrow aspirate was cellular with many erythroid and megakaryocytic elements. A chest radiograph was normal. An electrocardiogram showed nonspecific changes. Serum creatinine was 3.4 mg/dl. Urinalysis showed 2+ proteinuria and a brain scan showed no changes from previous examinations. She received packed red blood cells, and was begun on methylprednisolone 60 mg q.d. She improved gradually and was discharged after a 2 week hospitalization on folate and pyridoxine.

Three weeks later, she returned with a left hemiparesis and aphasia. She had a temperature of 104°F, a hematocrit of 25% with a microangiopathic peripheral blood smear, and a platelet count of 53,000 mm^3. Serum creatinine was 6.3 mg/dl. Coagulation studies and a muscle biopsy were normal. She was begun on high dose steroids with resolution of her neurologic, renal and hematologic problems over the next several weeks. She was discharged after an 18 day hospitalization and continued on prednisone 75 mg q.d. with gradual tapering of the dose.

Three months later, she was hospitalized for a pulmonary embolus, documented by angiography, and was treated with heparin. Her platelet count went from 162,000 mm^3 on admission to 46,000 mm^3 over a 5-day period while on heparin. Values returned to normal after heparin was discontinued. She was discharged on coumadin and prednisone 60 mg q.d.

At last follow up, 2.5 years after diagnosis of TTP, her hematologic status was normal. She continues taking prednisone 15 mg q.d.

Comment: This patient exhibited recurrent episodes of TTP which in both instances responded dramatically to steroid therapy. Recurrent attacks of TTP occur in approximately 7.5% of the reported cases.

Case 3

J.B. was a 56-year-old white female with known arthritis (non-rheumatoid) managed with aspirin. She was allergic to sulfonamides. Five months before her Johns Hopkins Hospital admission, she noted easy bruisability and petechiae and 4 months before admission developed a "chest cold" which failed to resolve. She was hospitalized elsewhere one month before admission, complaining of shortness of breath and headaches. Her hematocrit value was 26% and initial platelet count 200,000 mm^3 which dropped to 55,000 mm^3 several days later. Serum creatinine was 5.1 mg/dl and urea nitrogen 63 mg/dl. Urinalysis revealed numerous red blood cells. A Coombs test, serum fibrinogen, partial thromboplastin time (PTT) and ANA were normal. She received blood transfusions (four units), prednisone 40 mg q. 8 hours, and was hemodialyzed after her renal function deteriorated. Her condition failed to improve and she was transferred to Johns Hopkins Hospital for evaluation.

Physical examination revealed a blood pressure of 180/95, pulse of 80, and respirations of 14 per minute. Skin examination revealed scattered petechiae over the extremities and ecchymoses on the forearms. Petechiae were present on the palatal mucosa. Chest examination demonstrated rales bilaterally and decreased breath sounds at the lung bases. There was mild pitting edema of the lower extremities. Neurologic examination showed some recent memory loss and difficulty with serial 7s. No localizing findings were observed.

Laboratory findings included the following: Hematocrit value 29%, white blood count 10,100 mm^3, platelets 59,000 mm^3, serum urea nitrogen 166 mg/dl, calcium 7.8 mg/dl, phosphorus 6.3 mg/dl, total serum protein 4.3 g/dl, and albumin 2.6 g/dl. Rheumatoid factor was positive at a titer of 1:320. Bilirubin, SGOT, an ANA test, and a Coombs test were normal. Coagulation studies including prothrombin time (PT), PTT, fibrinogen and tests for FDP-fdp were negative. C4 was 8 mg/dl (normal 11–75 mg/dl) and C3 was 35 mg/dl (normal 55–120 mg/dl). Urinalysis revealed 3+ protein and numerous red blood cells. A peripheral blood smear showed occasional fragmented red blood cells. An electrocardiogram showed ST elevation in lead 1 and aVL and ST depression in leads III and aVF raising the possibility of inferior lateral wall myocardial ischemia.

The patient was anuric and hemodialysis and steroids were begun. She became progressively disoriented. On the 31st day of hospitalization she became abruptly nonresponsive and comatose. Her platelet count was 39,000 mm^3 and coagulation profile normal (PT, PTT, fibrinogen and FDP-fdp). EMI scan demonstrated a probable pontine hemorrhage. The patient died on the 36th hospital day.

Autopsy examination revealed microscopic findings consistent

with TTP including conspicuous microvascular thrombi involving the brain and kidney, with less severe involvement of the pancreas, adrenal glands and other viscera. There was no evidence of vasculitis.

Comment: This case demonstrates a pattern of visceral involvement different than that usually seen, with the brain and kidneys displaying the most severe pathologic findings. It resembles the adult hemolytic-uremic syndrome (HUS) which appears to overlap in many instances with TTP (90, 128). The clinical picture was suggestive of some type of immunological disease such as SLE with renal failure, or a vasculitis.

Case 4

S.N. was a 19-year-old obese white female with a history of easy bruisability for at least 6 months, and a 3-week history of weakness and fatigue. Approximately 1 month prior to admission she experienced an episode of aphasia and altered consciousness which lasted 15 minutes. One week prior to admission her hemoglobin was 5 g/dl, platelet count of 16,000 mm^3, and reticulocyte count 7.2%. She developed severe bifrontal headaches and was transferred to the Johns Hopkins Hospital.

On admission physical examination revealed a pale, slightly jaundiced, uncooperative female who complained of severe frontal headaches. Her heart rate was 105/minute; remaining vital signs were normal. Small bruises were noted on her extremities and blood was present within her vagina. Retinal hemorrhages were present bilaterally. The spleen was palpable.

Admission laboratory studies included a hematocrit value of 14.5%, white blood cell count of 7,000 mm^3, and platelet count of 9,000 mm^3. A peripheral blood smear showed many misshapen and fragmented red blood cells; polychromatophilic, stippled, and occasional nucleated red blood cells. A chest radiograph was normal; electrocardiogram was normal with the exception of sinus tachycardia. Urinalysis showed many red blood cells; however, the patient was menstruating. Bilirubin was 2.8 mg/dl (direct 0.7 mg/dl), creatinine 1.0 mg/dl, haptoglobin 0, hemopexin 35 mg/dl (normal 50–100 mg/dl), and an LE preparation, a test for rheumatoid factor and a direct Coombs test were negative. Liver enzymes, alkaline phosphatase, C3, C4, total serum protein, PT and PTT were normal. The fibrinogen was 240 mg/dl and FDP-fdp were weakly positive at a titer of 1:16.

The patient was begun on prednisone 150 mg q.d. and was given two units of packed red blood cells. Her headaches disappeared promptly. However, her hematologic status failed to improve, and at the end of 1 week of hospitalization her hematocrit value was 18.5% and platelet count 28,000 mm^3. She received a 12 unit plasma infusion over a period of 12 hours with no observable effect. After two weeks of hospitalization aspirin 600 mg q.i.d. and dipyridamole (Persantine) 100 mg t.i.d. were begun. Sulfinpyrazone 400 mg q.d. given in divided doses was begun on the third week and prednisone was reduced to 70 mg q.d. The hematocrit value was 22.7% and platelets 45,000 mm^3.

She improved gradually and was discharged on prednisone, aspirin, sulfinpyrazone, Persantine, and Megace. Ten days later her hematocrit value was 32%, platelet count 93,000 mm^3, and reticulocyte count 8.2%. She was maintained on 30 mg q.d. of prednisone and continued to show gradual hematologic improvement. One month later hematologic values were within normal limits. After one year she is receiving no medication.

Comment: This patient with TTP exhibited hematologic abnormalities which appeared refractory to a host of therapies including steroids, plasma infusion, and antiplatelet drugs. She recovered but it is difficult to attribute her improvement to any specific agent. Why her disease did not progress is not apparent; but more cases of TTP-like syndrome have been observed over the past decade which exhibit variability in severity.[1]

Literature Review

Frequency

TTP is a rare disorder. Since 1960 approximately one case per year has been diagnosed at Johns Hopkins during which time yearly admissions ranged from 45,625 to 51,718.

Age/Sex (Figure 1)

Amorosi and Ultmann cited a 3:2 female:male ratio (6). Since 1965, 192 females and 78 males have been reported with TTP. Racial tendencies are difficult to evaluate, but since 1965 of the reported cases 81 were Caucasians and 25 blacks.

Most cases occur between the first and fourth decades with a peak incidence in the third decade. In this review cases spanned a broader range with a peak in the third decade (see Table 1). Occasional cases developed during infancy or the neonatal period (20, 120) and rare cases have been reported in patients over the age of 70 (40, 137).

Clinical Manifestations (Tables 1 and 2)

In addition to presenting with rather nonspecific constitutional symptoms including malaise, fatigue, and weakness (64 patients), nausea and vomiting (55 patients), and fever (37 patients), the most frequent chief complaints of patients were neurological (including headaches) (116 patients) or related to hemorrhagic problems (86 patients). Eighteen patients complained of antecedent upper respiratory tract symptoms and 12 of arthralgias or myalgias.

Thirty-two complained of abdominal pain, usually dull and generalized in quality; and 6 patients presented with anginal-type chest pain—most likely secondary to severe anemia.

These data are comparable to those observed by Amorosi and Ultmann (Table 1).

During their course 104 of 258 patients (40%) exhibited microangiopathic hemolytic anemia, thrombocytopenic purpura and/or other gross hemorrhagic signs, neurologic symptoms, fever, and

[1] A detailed table with all information on each of the 25 patients is available from the authors upon request.

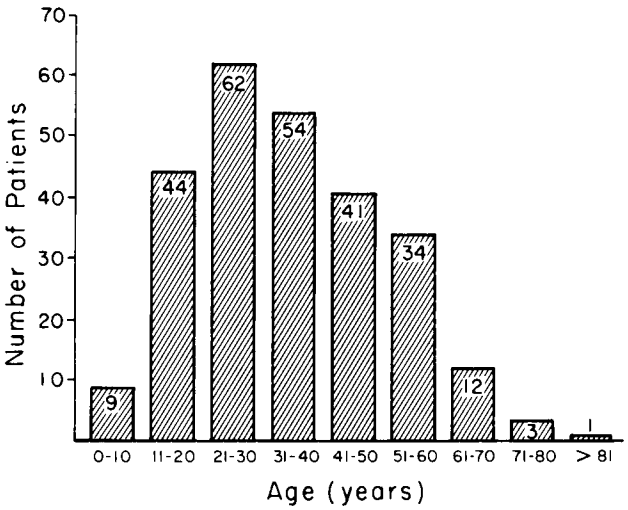

FIG. 1. Age, race and sex distribution in 270 patients with TTP. Sex: female, 192; male, 78. Race: White, 81; Black, 25.

TABLE 1. Presenting Chief Complaints in 225 Patients with TTP

	#	%	Amorosi and Ultman %
Neurologic (any)	116	52	60
Neurologic (headache only)	35	15	
Hemorrhagic	86	38	44
Malaise, fatigue, weakness	64	29	25
Nausea, vomiting, diarrhea	55	24	24
Fever	37	18	20
Abdominal pain	32	14	11
Flu-like syndrome	18	9	
Dark urine	13	6	
Arthralgia, myalgia	12	6	7
Chest pain	6	3	
Cough	6	3	
Icterus	5	2.5	9

TABLE 2. Incidence of the Pentad Features in 258 Patients with TTP

	#	%	Amorosi and Ultmann %
Microangiopathic hemolytic anemia	254	98	96
Thrombocytopenic purpura (or other bleeding)	214	83	96
Neurologic symptoms	218	84	92
Renal disease	196	76	88
Fever	152	59	98
Triad (anemia, purpura, neurologic)	192	74	
Pentad	104	40	

renal abnormalities. One hundred and ninety-two of 258 patients (74%) developed the classic triad, with all but three individuals manifesting a microangiopathic hemolytic anemia, 218 of 258 patients (84%) displaying neurologic symptoms and 214 of 258 patients (83%) developing hemorrhagic problems. Renal disease was present in 76% and fever in 59%.

Bleeding and Purpura

Skin was the overwhelming site of hemorrhagic manifestations in patients with TTP. In 171 of 214 patients with clinically apparent bleeding, petechiae, purpura, or ecchymoses of the skin were evident. Twenty-five patients had retinal hemorrhages; 30, gross hematuria; and 29, conjunctival or mucous membrane bleeding. Twenty-one patients manifested gynecologic bleeding, often as a presenting symptom, while 15 had gastrointestinal bleeding, and 13 had epistaxis. A single patient experienced hemoptysis.

Neurologic Manifestations (Table 3)

The most frequently observed neurologic problems included confusion (82 patients), headaches (68 patients), pareses (73 patients), and transient dysphasia or aphasia (73 patients). Unusual behavior or "altered" mentation were described in an additional 32 patients. Neurologic symptoms were usually transient and often recurrent.

Renal Manifestations (Table 4)

Gross or microscopic hematuria was the most frequent renal abnormality found. Roughly one-fifth of patients with hematuria had gross hematuria. Proteinuria was identified in 59% of patients

TABLE 3. Neurologic Manifestations in TTP (218 Patients)

	#	%
Headache	68	31
Confusion	82	37
Altered mental state	32	15
Paresis	73	33
Aphasia, dysphasia	73	33
Coma	45	20
Seizures	44	20
Paresthesias	31	14
Visual problems	31	14
Ataxia, vertigo	5	2.5
Syncope	2	

TABLE 4. Renal Manifestations in TTP (196 Patients)

	#	%
Hematuria (any)	149	76
Gross	30	15
Proteinuria (any)	116	59
2–5 g/day	3	
>5 g/day	3	
SUN >30 mg/dl and/or creatinine >2.0 mg/dl	89	45
SUN >50 mg/dl and/or creatinine >5.0 mg/dl	24	12
Acute renal failure	23	11.5

with renal disease. It was usually graded as 1+ or 2+ by dipstick. Six patients had documented proteinuria of over 2 g/day. Mild elevations of serum urea nitrogen and/or creatinine were also common (44). Twenty-three cases of acute renal failure were reported.

Other Organ Systems

Significant cardiac involvement may be more frequent than generally appreciated and can contribute to left sided congestive failure and sudden death (69). The latter probably occurs as a result of microthrombi and related tissue injury within the cardiac conduction system (163).

Pulmonary involvement in TTP (21, 85) is most likely secondary to cardiac or general fluid and metabolic problems seen in these patients (163).

Pancreatitis has been described (138), and rarely is the presenting manifestation of the syndrome. Mild pancreatitis may be the cause for the presenting complaint of abdominal pain noted in many patients (Table 1).

Ocular involvement is often noted (6, 100, 143). In Percival's review retinal hemorrhage was noted most frequently with choroidal hemorrhage, retinal detachment, and papilledema observed less (143).

Laboratory Findings

Hematologic

Microangiopathic hemolytic anemia is often severe. Eighty-nine percent (211/237) of the patients had hemoglobin values of less than 10 g/dl and 38% (90/237 patients) had values below 6.5 g/dl. TTP without anemia is unusual, although in rare instances the hemolytic process is compensated for fully (6). Three percent (6/237) of the patients in the current review had normal hemoglobin values.

Red blood cell indices are invariably normocytic and normochromic unless superimposed on a coincidental problem such as iron deficiency or an associated megaloblastic process. The peripheral blood findings in typical cases show numerous fragmented red blood cells (schizocytes) and other misshapen red blood cells. Polychromatophilia and basophilic stippling are often conspicuous, and nucleated red blood cells may be plentiful. In 53 cases the presence of nucleated red cells was noted. Reticulocyte counts (uncorrected as given) were with rare exception elevated. In 43.5% (78/179 patients) where reticulocyte counts were recorded, they ranged between 2 and 10% and in 35% (63/179 patients) of the reported cases were greater than 20% of the circulating erythrocytes. Six patients had reticulocyte counts of less than 2%.

The hemolytic anemia is characteristically Coombs negative. Since 1965 six cases have been reported in which the direct Coombs test has been positive (17, 26, 56, 62, 143, 160). In two cases the reaction was weak (17, 143); in one, the reaction was initially negative and on repeat was positive with complement present on the red cells (160) (this patient had an underlying mycoplasma infection); in one case IgA and C1 were detected on the erythrocytes (62); in a single case the positive reaction was described in a patient with SLE and TTP (56); and in another instance the positive reaction was associated with a positive LE preparation (26). With the possible exception of one case there is no evidence that the hemolytic anemia was immune in character (62, 131).

Other laboratory values indicating red cell hemolysis include elevation of LDH and plasma hemoglobin and decreased haptoglobin and/or hemopexin (1, 6, 78, 130, 150, 160).

White blood cell counts were increased in 56% (99/176) but in 40% (71/176) of the cases were normal ($4.2–10.5 \times 10^3/mm^3$). Leukopenia was described in only six cases. Differential counts were generally unremarkable; in those individuals with leukocytosis a left shift was often observed.

Severe thrombocytopenia is characteristic of TTP. Platelet counts less than 20,000 mm^3 were the most common in 56% (126/225 patients) with platelet counts between 20 and 60,000/mm^3 noted less often in 39.5% (89/225 patients). In a single instance the platelet count remained above 200,000/mm^3.

Bilirubinemia is common, usually due to elevation of the unconjugated fraction, secondary to red blood cell hemolysis. Seventy-nine percent in 122/155 patients in whom values were recorded had an elevation of total serum bilirubin above 1.5 mg/dl and in 41.5%, 64/155 patients, the values were greater than 3.0 mg/dl.

Coagulation Studies

This particular area has been one of controversy but a general pattern of abnormalities has emerged. The majority of patients with TTP have either normal or mildly deranged coagulation studies. Prothrombin times were normal in 88% (110/125); partial thromboplastin times were normal in 94% (100/106); and plasma fibrinogen was normal in 79% (107/137). In only seven cases was the plasma fibrinogen less than 100 mg/dl.

Fibrinogen-fibrin degradation products (measured with a variety of different techniques) were normal in 53% (35/67) and weakly positive in 23% (15/67). In 25% (17/67) FDP-fdp were present at a titer of greater than 1:32 or were more than 25 mg/dl. Jaffe et al reported 12 patients with TTP in whom they performed coagulation studies (86). They concluded that the majority of patients had normal or minimally altered coagulation studies

and that in those few in whom disseminated intravascular coagulation (DIC) was probably present, the alterations were probably secondary to systemic TTP.

Other Studies

Amylase elevations and associated evidence of pancreatitis were noted in two cases in this review (21, 138) and have been noted previously (6). In light of the pathologic involvement of the pancreas in TTP, it is surprising that they are not more often elevated. SGOT and SGPT may be elevated but the pathogenesis of these alterations is not clear. Liver and muscle involvement in TTP is minimal.

LE cell preparations were positive in five patients included in this review (4, 26, 56, 183) and ANA was positive in five instances (8, 48, 55, 133, 171). Both tests were positive concomitantly in only one patient (56). Positive ANA tests were associated with normal anti-DNA binding in 3/4 cases. Among the nine patients with these positive serologic studies only two had a clinical diagnosis of SLE (4, 56). Complement levels in 10 cases were normal (28, 43, 48, 68, 111, 133, 164, 167) and in another instance, were mildly diminished (115). Cameron and Vick described decreased plasma C3 in 5 of 10 patients with HUS or TTP during the acute phase of the illness (36). Rheumatoid factor has occasionally been observed (17, 59).

Premortem Tissue Findings

Approximately 72% of splenectomy specimens show intravascular hyaline thrombi. Among 68 splenectomy specimens, 49 showed characteristic pathologic changes (5, 13, 17, 37, 53, 56, 58, 60, 68, 72, 83, 89, 95, 110, 122, 132, 145, 160, 170–172, 188, 199, 200, 202, 203).

Biopsy of gingival tissue showed typical changes of TTP in 45% (18/40) (8, 26, 28, 67, 72, 110, 115, 171, 175). A recent review of gingival biopsies in patients with TTP revealed a lower diagnostic yield (39%) and warned of the nonspecificity of the histologic changes (73).

Bone marrow aspirates reported in 105 patients, showed hypercellular marrows with erythroid hyerplasia and prominent megakaryocytes. Bone marrow biopsies yielded "positive" findings in six instances (20, 78, 99, 150, 169, 194). Bone marrow biopsies were performed in four patients in our series and one showed microthrombi. In reviewing bone marrow sections from our 17 autopsied cases, hyaline thrombi were identified in 11 instances, but were conspicuous in only three. Bone marrow particles were reported positive in 8/17 cases at the time of Amorosi and Ultmann's review but subsequently, positive findings appear to be infrequent. Positive biopsy findings have been reported in rare instances from skin (26, 127), muscle (26, 72), lymph node (37, 56, 60, 66) and kidney (59, 110, 193, 198). Patients with TTP rarely have lymphadenopathy. If lymph nodes are palpable, they may prove to be of diagnostic value. Liver biopsies have not shown diagnostic changes.

Clinical Course and Therapy

Survival is the most notable difference between patients with TTP reported since 1965 and those reviewed by Amorosi and Ultmann. Of the 271 cases previously reviewed, there were 27 survivors (approximately 10%). Of these, 14 were thought to have either hemolytic-uremic syndrome or systemic lupus erythematosus, with only 13 survivors having classic TTP (approximately 5%) (6). Of the 275 cases in the present review there were 127 survivors (46%). It is probable that an increased awareness of TTP has led to both earlier detection and recognition of milder forms of the syndrome over the past decade. In addition, improved supportive therapeutic measures and newer modes of therapy directed specifically at underlying pathophysiologic alterations, such as antiplatelet therapy and plasmapheresis, may have contributed to these improved survival statistics.

Although TTP is usually thought of as a fulminant disorder, many patients have recurrent episodes of several months duration before succumbing. Sixty of 127 patients (47.5%) who died of disease had a hospital course of less than seven days. Forty-five patients (36%) died between 2 and 4 weeks of hospitalization and 22 (17%) after a month or more of illness.

Seventy-four of 105 patients who recovered had courses from several weeks to several months. Eight recovered in less than 1 week, 23 in 1 to 2 weeks and 37 in 2 to 4 weeks.

Relapses occurred in 18/132 patients (7.5%) and approximately 50% died following such a recurrence (17, 19, 22, 50, 53, 56, 65, 68, 72, 79, 83, 84, 120, 133, 151, 164, 171).

A plethora of therapeutic combinations have been utilized, making meaningful evaluation virtually impossible (27, 31, 32, 49, 76, 97, 126, 129, 158, 166, 186, 191). Identical combinations used in at least 12 patients which were associated with better than average survival (greater than 46%) include steroids and splenectomy, 19/29 patients (65%), steroids, splenectomy and antiplatelet drugs, 8/14 patients (54%), steroids and plasma exchange therapy 7/13 patients (54%) and steroids, splenectomy and average molecular weight dextran 10/12 patients (82%). Among all patients receiving steroids 50% lived. For patients undergoing splenectomy this

figure is 62%; for those receiving antiplatelet therapy, 60%; and for patients undergoing exchange transfusion or plasma infusion, 70%. In patients who received multiple therapies there appeared to be a clinical response temporally related to one of the agents such as steroids, antiplatelet drugs or plasma infusion (26, 28, 33, 150, 171). Recent reports question the value of antiplatelet agents in TTP (27, 126) and our own experience of failure in four patients is disconcerting.

A recent therapeutic measure is some form of blood or plasma exchange (partial or total body exchange), and plasma infusion. Forty-seven of sixty-seven patients (70%) managed with plasma therapy (exchange, pheresis or infusion) survived (8, 26, 28, 33, 47, 50, 56, 57, 66, 82, 103, 110, 112, 114, 127, 137, 150, 155, 162, 168, 170, 171, 182, 185, 188, 195, 197, 201, 202). All but six of these patients received concomitant corticosteroids (26, 28, 103, 127, 150) and many other therapeutic agents. In some instances immediate improvement appeared directly after the plasma therapy (28, 32, 127, 171) whereas in other patients the improvement appeared unrelated (26, 150, 171). Some patients with TTP in coma, on treatment with steroids without response, promptly regained consciousness during the plasma procedure (26, 28, 112, 114, 171). In many of these patients, there was also reversal of the hemolytic anemia and thrombocytopenia. In others there was only partial improvement in their hematologic status. In some patients the favorable response lasted only a few days. Reinstitution of plasma therapy has been observed to result in return of CNS function. In a few patients plasma infusion alone in the absence of any additional medications has appeared to be beneficial (32, 103). Thus some form of plasma therapy may be an effective means of reversing TTP in some patients (27, 76, 126).

Administration of prostacyclin (PGI_2), prostaglandin X, and epoprostenol in three patients (47, 48, 106, 158) and in four other cases (unpublished) was unsuccessful.

In a recent series 13 of 15 patients who had splenectomy survived and were disease free (87%) at the time of reporting (54).

At present a practical therapeutic approach may be the following:

a) If the patient is relatively stable and free of or with only minor central nervous system manifestations, e.g., mild headache, the initial treatment should be with corticosteroids (100–200 mg/day prednisone or equivalent); in those patients with hepatic insufficiency, methyl-prednisolone in the same dose. In our experience patients who respond to corticosteroids do so within 24–72 hours.

b) If the patient presents with major neurologic disturbances such as coma, or the patient fails to respond to high dose steroids alone, some type of plasma therapy should be given. In our experience plasma exchange, accomplished by plasmapheresis and replacement with fresh frozen plasma, has yielded the best results. The volume removed and replaced is 35–40 ml/kg/exchange (requiring 10–15 units of fresh frozen plasma for each exchange). The frequency of plasma exchange is determined by the clinical response and by changes in serum lactic acid dehydrogenase (LDH) (185). Failure to reduce the LDH activity below 700 IU/dl indicates insufficient plasma was exchanged (185). The frequency and duration of plasma therapy has not been defined. This therapy should be guided by clinical status, serum LDH, the reticulocyte count, fragmented RBCs in peripheral smear, the platelet count and hematocrit value. If the patient fails to respond after daily or twice daily plasma exchanges after 7 days no benefit can be expected.

c) If the patient responds initially to plasma exchange and repeatedly relapses, the addition of a single antiplatelet agent or a combination of antiplatelet agents (aspirin, dipyridamole, sulfinpyrizone) should be considered.

d) If the patient fails to respond to the combination of steroids, plasmapheresis, plasma exchange and antiplatelet agents, then splenectomy should be considered.

There is little evidence for the use of heparin, dextran, magnesium or cytotoxic immunosuppressive agents.

There are at least three reasons why survival in TTP is better than it was 10–15 years ago: 1) the diagnosis is being made earlier in the course of the illness; 2) general supportive medical care is significantly better now than it was earlier; 3) plasma therapy in the form of exchange, infusion or in combination with pheresis.

Etiology-Pathogenesis

The precipitating causes of TTP are probably multiple. Drugs, toxic substances, and infectious agents have appeared to trigger the syndrome. A variety of immunologic disorders have been associated with TTP or TTP-like illnesses. An unexpectedly large number of cases have been described in the obstetric literature. Underlying malignancy has seldom been documented (24, 41). Rare instances of TTP occurring in siblings (68, 135, 141, 198) and in husband and wife simultaneously (199) have occurred.

The majority of cases (greater than 90%) develop without an apparent causal event or an underlying disease process.

Drugs and Toxins

In the present review series six patients were thought to have developed TTP in relation to the administration of a variety of drugs (1, 22, 40, 81, 140). In many other cases drugs may have

precipitated the illness; however, the association may have been fortuitous (14, 137, 160, 164, 171, 185, 187). In two instances TTP developed during the administration of penicillamine (1, 81) and in two cases, related to sulfa compounds (40). One case appeared related to both penicillin and ampicillin administration in a patient with recurrent episodes following usage of each drug (140) and in another, episodes of TTP developed on three different occasions following the administration of penicillin twice and neomycin once (22). Sulfonamides and penicillin have been implicated in cases antedating this review as have iodine, chloropropamide, procainamide, and oxyphenarsine (6). Several cases have been reported in which oral contraceptive agents were thought implicated (54, 196).

Two reports have documented TTP following vaccination; one following influenza vaccination (25) and the second, after polio vaccination in a seven-month-old child (20).

Toxins have rarely been suggested as possible etiologic agents. Pilz et al described a case in which chloronaphthalene in varnish was thought to be the causative agent (148) and Stonesifer reported a case of TTP following carbon monoxide poisoning (184). A single case of TTP developed following a dog bite (109).

Infectious Agents

Berberich reported two cases in which Coxsackie B virus was implicated (14). Both occurred in pediatric patients. Mycoplasma was implicated in a single case reported by Reynolds (160) and in 1969, Mettler isolated a Microtatobiote (order Rickettsaiales) from two patients with HUS and a third with TTP (115). Bacteria have not been described as causative agents.

Nonspecific viral-type upper respiratory tract syndromes have preceded TTP in at least 18 cases (Table 1).

Immunologic Diseases

Convincing cases of SLE associated with TTP are rare; five cases were reported among this review population. We feel only three are acceptable as described. Alpert's case report (4) and the first of two cases (55) described by Dekker et al with SLE were diagnosed clinically with serologic confirmation prior to the development of TTP. Both patients died of TTP and autopsies revealed microvascular thrombi unassociated with vasculitis. Additionally, in Alpert's case, light microscopic and immunofluorescent findings in the kidneys were consistent with SLE. The second case of Dekker et al is consistent with the concomitant development of TTP and SLE. TTP was confirmed histologically in both the spleen and lymph nodes. Positive cell preparations and elevated ANA titers were noted during the acute illness. Ramkissoon described a patient who died with non-bacterial thrombotic endocarditis (NBTE) and thromboemboli (153). Serologic studies for SLE were negative and a microangiopathic anemia was not described.

In 1964 Levine and Shearn retrospectively reviewed 151 cases of TTP and recorded findings suggestive of SLE in 23% (34 cases) (100). In 25/34 instances this suggestion was based on the presence of "Libman-Sacks endocarditis" only, and the diagnosis of SLE was otherwise unsupported. As Amorosi and Ultmann noted (6), the precise character of the endocarditis in many of these cases is questionable and most probably represents NBTE and not Libman-Sacks endocarditis (vide infra). Only 5 of the 34 patients had positive LE cell studies.

An association with Sjögren's syndrome has been suggested in three patients reported by Steinberg et al (181). The diagnosis of TTP in their cases was not certain, and by strict criteria cannot be substantiated.

Other immunologic diseases (131) have antedated the development of TTP including rheumatoid arthritis (59, 66), ankylosing spondylitis (6), polymyositis (112), Graves' disease (127) and immune thrombocytopenic purpura (ITP) (152, 206).

Fagiolo described a patient with TTP who displayed pancytopenia and evidence of an autoimmune hemolytic process (62). IgA and C1 were identified on red blood cells, antileukocytic antibodies were demonstrated, and a thromboagglutination test was positive. This patient had no evidence of an underlying immunologic disorder. This is the only instance in the present review series in which thromboagglutinins were found. In other cases investigations for platelet antibodies have been negative (8, 20, 89, 150, 171). In a single case Morrison and McMillan demonstrated elevated platelet-associated IgG (124). In another case Meister et al, described immune complexes in a patient with TTP which were composed of IgG and platelet membrane antigens (114). Others have failed to demonstrate immune complexes in TTP (8, 43, 124).

Few immunologic tissue studies have been performed and in only three instances in which SLE was not coexistent with the findings suggestive of an immune pathogenesis. Mant et al demonstrated IgM, complement, and fibrin within thrombotic TTP vascular lesions (107). Weisenburger et al noted similar findings in another case (200), and Ryan et al detected IgG and C^1 in TTP vascular lesions in the spleen (171). Others have failed to demonstrate IgG or complement within TTP vascular lesions (43, 52, 64).

Obstetric Cases

Twenty-five cases (9%) in this review occurred in pregnant or postpartum females (12, 17, 28, 33, 39, 68, 83, 95, 103, 110, 122, 133, 152, 161, 172, 193, 196, 197, 202). The majority were in their third trimester with three cases appearing in the postpartum period, four during the first trimester, and six during the second trimester. Ten of these patients died and their overall response to therapy was no different from others with TTP. Coagulation studies in these patients were usually normal and in no instance strongly suggestive of DIC. The difficulty in distinguishing DIC from TTP in the obstetric patient is important for therapeutic reasons (204).

Similarly eclampsia can be confused with TTP (175).

The clinical course of the TTP varied widely within this group. In seven cases stillborn infants were delivered (17, 26, 33, 110, 152). Some of these patients improved subsequently (17, 110, 193) whereas others deteriorated (64, 110, 196). Evidence of TTP in one instance occurred immediately following Caesarian section (13). In another patient TTP developed during gestation, was treated and resolved, and the patient subsequently delivered without complication (83). Occasional patients responded favorably only to relapse months later while not pregnant (133, 152).

Wurzel described a pregnant female who died of TTP (202). At autopsy a macerated fetus and placenta were present. TTP thrombotic lesions were identified within the placenta but not the fetus. The possibility that a "factor" responsible for TTP might be able to cross the maternal-fetal barrier was suggested.

Coagulopathy

Evidence to date fails to support an underlying coagulopathy as the pathogenetic mechanism in TTP (61, 86). Laboratory

evidence of DIC when present is most likely secondary in nature and usually mild in degree (86). In a single case an abnormal fibrinogen by immunoelectrophoresis was documented during an episode of TTP, which subsequently reverted to normal after resolution of the illness (164). An abnormality within the fibrinolytic system has been suggested (96) but there is no supportive evidence to date. Studies have shown that the turnover rate of fibrinogen is essentially normal in TTP whereas platelet turnover is markedly accelerated (14, 61, 80, 89).

Platelet consumption appears to be an integral component of the pathophysiology in TTP. The possibility of a primary endothelial insult with secondary platelet thrombosis has been suggested (64, 119, 132). There is no direct evidence to support this contention, but it is consistent with the pathologic findings, and substances have been identified which when deficient might act as mediators. A factor similar to prostacyclin, a known natural inhibitor of platelet aggregation, which is probably synthesized in vascular endothelial cells, might be responsible for mediating this sequence of events (156, 157). Lian et al recently reported the presence of a platelet aggregating factor in patients with TTP which appeared to be inhibited by an unidentified component in normal plasma (103). Their observations suggested that some cases of TTP might be due to a deficiency of a plasma inhibitor to such a platelet aggregating factor. Further investigation into this possibility is warranted (102).

A report by Upshaw suggests the existence of a plasma factor which may reverse microangiopathic hemolysis and thrombocytopenia (192). He described a patient who had multiple episodes of microangiopathic anemia and thrombocytopenia beginning at 6 months of age and continuing throughout life. These episodes were reversed by plasma, suggesting a congenital deficiency of an unknown substance. The rationale of exchange transfusion or plasma infusion in patients with TTP is based on the possibility of deficiency of a plasma factor as suggested in Upshaw's report. Subsequent studies revealed decreased levels of a functionally normal "cold-insoluble globulin" in this patient (159). This substance has been shown to mediate the uptake of gelatin-coated particles by the reticuloendothelial system, and may possibly aid in removal of circulating debris after tissue insult. Decreased levels of this protein have followed experimental DIC (159). Other patients with TTP studied by Rennard and Abe had normal levels of "cold-soluble globulin" (159). Levels appeared normal in Upshaw's patient while in remission.

Pathology

Originally thought by Moschcowitz to represent congealed erythrocytes (125), the thrombus in TTP is comprised chiefly of platelets with lesser amounts of admixed fibrin (11, 15, 64, 75, 133). Although Craig and Gitlin (52) demonstrated fibrin and not platelets by immunofluorescent techniques, the majority of investigators have documented platelet aggregates within the lesion (11, 75, 133).

The vascular lesion per se is nonspecific. It consists of a bland platelet-fibrin mixture in varying stages of organization, occurring chiefly at the level of the anteriolar-capillary junction. In the early microthrombus one usually finds an intraluminal endothelial-adherent platelet aggregate. As fibrin is incorporated it is initially detected at the perimeter of the central platelet core and in the later lesions appears admixed in a more haphazard fashion with platelet and other cellular elements (133). The underlying vessel shows no evidence of vasculitis. The microaneurysm formation described by Orbison (139) is nonspecific and probably represents dilatation of the vessel segment proximal to the occlusive thrombus (190). The subendothelial pre-thrombotic lesion described by Gore (75) probably represents a stage in the organization of the intraluminal thrombus (15, 64, 190). Umlas has emphasized the nonspecific nature of glomerular structures, noting their presence in other disorders such as glomerulonephritis, DIC and lupus nephritis (189). Our review of 17 autopsies from patients with TTP supports these views.[2]

Although the individual thrombotic lesion is nonspecific in character, the florid disseminated nature of the process is quite distinctive and in most cases, separable from the pathologic findings in DIC where fibrin thrombi are much rarer and usually difficult to detect (165).

Just as the clinical manifestations vary from case to case in TTP, so too do the distribution of microthrombi at autopsy. In order of frequency the most severely involved organs include pancreas, adrenal glands, heart, brain and kidney (15). On a grading scale of 1–4+, as previously described (163), we found 3–4+ involvement of the pancreas in 11 of 17 cases, of the adrenal glands and kidney in 10 of 17, of the brain in 7 of 13, and of the heart in 8 of 17. Other organs are variably involved to a lesser degree and virtually all organs examined histologically in our series showed the presence of microthromboses, including thymus, appendix, retina, pituitary gland, and gall bladder. Notably spared in the disseminated thrombotic process are the lungs and liver which show only rare thrombi even in the severest cases. Despite the emphasis in the literature on splenic histology in the antemortem diagnosis of TTP, this organ is relatively mildly involved in the TTP process (15, 64). We found 3–4+ (163) involvement in 3 of 17 autopsied cases, 1–2+ involvement in 10 of 17, and absence of histologic involvement in four patients.

In the face of the widespread microthrombotic process, visceral organs tend to show relatively mild parenchymal changes, mainly focal areas of necrosis and hemorrhage. Discrete infarcts are unusual and when present, as in the brain, are usually hemorrhagic (41, 187).

A recent study emphasized respiratory dysfunction in TTP but found little to suggest TTP involvement of the lungs as the primary cause for such symptoms (21). On the basis of our own studies and others, respiratory problems in these patients are

[2] A complete tabulation of autopsy findings is available from the authors upon request.

most likely due to severe TTP cardiac disease and/or anemia-related high cardiac output failure (163).

Furthermore, in serial histologic studies of the cardiac conduction tissues we found microthrombi in 7 of 10 examined, which appeared clinically responsible for fatal arrhythmias in 2 patients (163). Vitally situated thrombotic lesions within the heart may be responsible for death in these patients more often than is generally appreciated (69, 87, 163). The same is probably true of critically located CNS lesions.

Associated Non-Bacterial Thrombotic Endocarditis (NBTE)

Twenty-eight cases of NBTE in association with TTP were reviewed by Amorosi and Ultmann (6). Since then only three such cases have been described (153, 181, 196). Only one case is convincingly shown to have both TTP and NBTE (196). These authors pointed out the larger sized emboli and discrete infarcts related to the NBTE which were distinct from the smaller microthrombotic lesions of TTP. We noted this association in 2 of our 17 autopsied cases. NBTE with systemic embolization can mimic many of the features of TTP (6, 153, 181).

Differential Diagnosis

Other disease processes which often enter into the differential diagnosis of TTP include SLE, autoimmune hemolytic disease (AIHD), Evan's syndrome, ITP, NBTE and DIC. The hemolytic anemia seen in SLE, AIHD and Evan's syndrome is Coombs positive and a peripheral smear will show many spherocytes. This is in contrast to TTP which almost always is Coombs negative and in which the microangiopathic nature of the hemolytic anemia is manifested in the peripheral smear as numerous schizocytes. Careful examination of a peripheral blood smear may be very helpful in suggesting the diagnostic possibility of TTP. ITP is usually not difficult to rule out since it is essentially manifested by thrombocytopenia and associated bleeding problems. Evidence of a multisystem disease process is usually lacking and microangiopathic hemolysis is not seen. SLE is a multisystem disorder which may manifest anemia (often Coombs positive) and thrombocytopenia. Serologic studies indicative of an autoimmune process are diagnostically discriminating although it has been mentioned previously that SLE and TTP may coexist. In the presence of a lupus-related vasculitis, microangiopathic erythrocyte changes may be seen making the antemortem distinction between SLE and TTP reliant primarily on serologic studies. When unusual diagnostic problems such as this arise, a more aggressive approach to tissue studies is indicated. Bone marrow, gingival and lymph node biopsies might be helpful in suggesting TTP. Skin, muscle or kidney might yield changes supportive of SLE.

NBTE and DIC may be associated with microangiopathic changes in the peripheral smear and may have multisystem manifestations. Patients with TTP generally do not exhibit laboratory coagulation findings as seen in DIC and when they do, alterations are usually mild. There is usually an apparent underlying disorder in patients with DIC such as carcinomatosis or sepsis. This is exceptional in patients with TTP.

Whereas NBTE does display multisystem manifestations similar to TTP, it usually develops in patients with an underlying debilitating disease. Patients with TTP are usually healthy prior to their illness. Thrombocytopenia and striking microangiopathic hemolysis are usually not features of NBTE. NBTE may develop in patients with TTP.

Subacute bacterial endocarditis (SBE) may present a picture similar to that of TTP (13) although the hematologic alterations seen in TTP are usually lacking. Positive blood cultures would confirm the diagnosis of SBE. Patients with TTP are not septic, as a rule, upon presentation, but may become so during the later stages of their illness.

In the pregnant patient the differential possibilities broaden and include pre-eclampsia (175), septic abortion (204), and other gynecologic complications which lead to DIC (122).

Hemolytic Uremic Syndrome (HUS)

Although this should be included in the differential diagnosis of TTP, we feel, as do others (90, 190), that HUS is closely related to TTP and that a spectrum of illnesses exists, ranging from the typical HUS process involving children and predominantly the kidneys, to a syndrome in adults of a similar nature, but in many cases involving other organ systems. With the exception of the difference in age of the population of patients afflicted, HUS and TTP have many common features. The onset is abrupt in previously healthy people; bleeding with striking purpura is observed at presentation; findings in the chemistry, hematology and coagulation laboratories are very similar (blood urea nitrogen more prominently elevated in the HUS); and histology of the affected organs is identical. Treatment is essentially the same for both illnesses.

A report by Hellman et al (82) described HLA identical siblings, one of whom died of TTP while the second survived what appeared clinically as HUS. The relationship between HUS and TTP is another poorly understood facet of the TTP syndrome.

Summary

The syndrome of thrombotic thrombocytopenic purpura was reviewed in a total of 275 patients. Two hundred fifty patients were previously reported in the literature from 1964 to the present. Twenty-five patients not previously reported who were diagnosed at The Johns Hopkins Hospital from 1930 to the present are presented. The pentad of features that classically highlight the syndrome, fever, hemolytic anemia, thrombocytopenic purpura, transient or permanent central nervous system signs, and renal disease, were commonly observed. The frequency and characteristics of the hematologic, biochemical, and ante and postmortem histologic laboratory studies were similar to those observed in the past. Thorough examination of the heart, as performed in the local series of patients, revealed a previously unappreciated high frequency of intravascular thrombotic lesions within the cardiac conduction system.

The antemortem diagnosis is reliant on the multisystem clinical signs and symptoms in conjunction with a microangiopathic hemolytic anemia and thrombocytopenia. Laboratory findings are generally nonspecific and tissue biopsy findings most often unrewarding. The differential diagnosis included other multisystem disease processes such as: systemic lupus erythematosus, subacute bacterial endocarditis, immune thrombocytopenic purpura, non-bacterial thrombotic endocarditis, and disseminated intravascular coagulation.

The hemolytic uremic syndrome and TTP exhibit overlapping features and are probably related.

The etiology of the syndrome remains unknown, with the majority of cases occurring in otherwise healthy patients without underlying illnesses. In some instances, drugs, toxins, and infectious agents have been causally implicated. In exceptional instances, TTP has developed in patients with underlying immunologic diseases such as systemic lupus erythematosus, but in the majority of cases, evidence of an underlying immune pathogenesis has been lacking when sought. An unusually large number of cases have been described in obstetric patients, but these individuals are otherwise similar to other patients with TTP. Patients with toxemia of pregnancy are often difficult to differentiate from those with TTP. The toxemic patients usually do not have an abrupt onset of symptoms and usually do not have the striking hemolytic anemia seen in TTP. Because of therapeutic considerations this distinction is important.

The majority of patients with TTP display normal or mildly altered coagulation profiles. The presence of mild disseminated intravascular coagulation in these patients is probably a secondary phenomenon.

The inciting event may be endothelial damage with subsequent microthromboses, possibly related to a deficiency of an as yet unidentified platelet-aggregating inhibitor, or a plasma factor capable of reversing microangiopathic hemolysis and thrombocytopenia.

Although the clinical course in TTP is usually acute and fulminant, patients may manifest prolonged illnesses and recurrent bouts over a period of many years. Relapses or recurrent episodes of TTP were documented in 7.5% of the present review population.

In contrast to the early experience with TTP in which over 90% of patients succumbed to their disease, the cumulative experience since 1965 has shown significantly improved survival, *regardless* of the specific therapy employed, with 46% of all patients surviving. More dramatic has been the recent experience with exchange transfusion or some mode of plasma therapy in managing patients with TTP. Although additional studies are required to identify the optimal way to employ plasma therapy (infusion, exchange transfusion or pheresis), information and experience presently available has allowed us to outline a reasonable therapeutic plan. Although the use of plasma therapy is clearly indicated in the treatment of patients with TTP, particularly those with significant CNS signs, because of the rarity of the disorder, it may require some time before the magnitude of the longterm benefits can be absolutely identified. From existing data, it is clear that corticosteroids or corticosteroids and plasma therapy are the initial treatments of choice for this disease.

References

1. Ahmed, F., Sumalnop, V., Spain, D. M. and Tobin, M. S.: Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. Arch. Intern. Med., *138:* 1292, 1978.
2. Aita, J. A.: Neurologic involvement of thrombotic thrombocytopenic purpura. Nebraska Med. J., *58:* 76, 1972.
3. Allanby, K. D., Huntsman, R. G. and Sacker, L. S.: Thrombotic microangiopathy. Recovery of a case after heparin and magnesium therapy. Lancet, *1:* 237, 1966.
4. Alpert, L. I.: Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. Report of a case with immunofluorescence investigation of vascular lesions. J. Mount Sinai Hosp. N.Y., *35:* 165, 1968.
5. Amir, J. and Krauss, S.: Treatment of thrombotic thrombocytopenic purpura with antiplatelet drugs. Blood, *42:* 27, 1973.
6. Amorosi, E. L. and Ultmann, J. E.: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine, *45:* 139, 1966.
7. Amorosi, E. L. and Karpatkin, S.: Antiplatelet treatment of thrombotic thrombocytopenic purpura. Ann. Intern. Med., *86:* 102, 1977.
8. Ansell, J., Beaser, R. S. and Pechet, L.: Thrombotic thrombocytopenic purpura fails to respond to fresh frozen plasma infusion. Ann. Intern. Med., *89:* 647, 1978.
9. Aronson, S. M.: Clinicopathologic Conference. Dis. Nerv. Syst., *30:* 493, 1969.
10. Aster, R. H.: TTP: New clues to the etiology of an enigmatic disease. N. Engl. J. Med., *297:* 1400, 1977.
11. Baehr, G., Klemperer, P. and Schifrin, A.: An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of

capillaries and arterioles. Trans. Assoc. Amer. Physicians, *51:* 43, 1956.
12. Barrett, C. and Marshall, J. R.: Thrombotic thrombocytopenic purpura. Obstet. Gynecol., *46:* 231, 1975.
13. Bayer, A. S., Theofilopoulos, A. N., Eisenberg, R., Friedman, S. G. and Guze, L. B.: Thrombotic thrombocytopenic purpura-like syndrome associated with infective endocarditis. JAMA, *238:* 408, 1977.
14. Berberich, F. R., Cuene, S. A., Chard, R. L. Jr. and Hartmann, J. R.: Thrombotic thrombocytopenic purpura: Three cases with platelet and fibrinogen survival studies. J. Pediatr., *84:* 503, 1974.
15. Berkowitz, L. R., Dalldorf, F. G. and Blatt, P. M.: Thrombotic thrombocytopenic purpura. A pathology review. JAMA, *241:* 1709, 1979.
16. Berman, N. and Finkelstein, J. Z.: Thrombotic thrombocytopenic purpura in childhood. Scand. J. Haematol., *14:* 286, 1975.
17. Bernard, R. P., Bauman, A. W. and Schwartz, S. I.: Splenectomy for thrombotic thrombocytopenic purpura. Ann. Surg., *169:* 616, 1969.
18. Bernstock, L. and Hirson, C.: Thrombotic thrombocytopenic purpura. Remission on treatment with heparin. Lancet, *1:* 28, 1960.
19. Birgens, H., Ernst, P. and Hansen, M. S.: Thrombotic thrombocytopenic purpura: Treatment with a combination of antiplatelet drugs. Acta. Med. Scand., *205:* 437, 1979.
20. Blecher, T. E. and Raper, A. B.: Early diagnosis of thrombotic microangiopathy by paraffin sections of aspirated bone marrow. Arch. Dis. Child, *42:* 148, 1967.
21. Bone, R. C., Henry, J. E., Petterson, J. and Amarc, M.: Respiratory dysfunction in thrombotic thrombocytopenic purpura. Am. J. Med., *65:* 262, 1978.
22. Boswell, D. C. and Sierra, G.: Probable 16-year course in a patient with thrombotic thrombocytopenic purpura. Ill. Med. J., *145:* 29, 1974.
23. Brain, M. C.: Microangiopathic hemolytic anemia. Ann. Rev. Med., *21:* 133, 1970.
24. Brook, J. and Konwair, B. E.: Thrombotic thrombocytopenic purpura associated with metastatic gastric carcinoma and a possible autoimmune disorder. Calif. Med., *102:* 222, 1965.
25. Brown, R. C., Blecher, T. E., French, E. A. and Toghill, P. J.: Thrombotic thrombocytopenic purpura after influenza vaccination. Letter. Br. Med. J., *2:* 303, 1973.
26. Bukowski, R. M., Hewlett, J. S., Harris, J. W., Hoffman, G. C., Battle, J. D., Silverblatt, E. and Young, I-Yen: Exchange transfusions in the treatment of thrombotic thrombocytopenic purpura. Semin. Hematol., *13:* 219, 1976.
27. Bukowski, R. M., Hewlett, J. S., Reimer, R. R., Groppe, C. W., Weick, J. K., Livingston, R. B.: Therapy of thrombotic thrombocytopenic purpura: An overview. Semin. Thromb. Hemostasis, *7:* 1, 1981.
28. Bukowski, R. M., King, J. W. and Hewlett, J. S.: Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. Blood, *50:* 413, 1977.
29. Burke, B. A. and Hartmann, R. C.: Thrombotic thrombocytopenic purpura: Two patients with remission associated with the use of large amounts of steroids. Arch. Intern. Med., *103:* 105, 1959.
30. Burr, W. A.: Thrombotic thrombocytopenic purpura. Proc. R. Soc. Med., *66:* 650, 1973.
31. Byrnes, J. J.: Recent treatment advances in thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *5:* 199, 1979.
32. Byrnes, J. J.: Plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *7:* 9, 1981.
33. Byrnes, J. J. and Khurana, M.: Treatment of thrombotic thrombocytopenic purpura with plasma. N. Engl. J. Med., *297:* 1386, 1977.
34. Cahalane, S. F.: Late recurrence of thrombotic thrombocytopenic purpura. Letter. Br. Med. J., *2:* 562, 1975.
35. Cahalane, S. F. and Horn, R. C.: Thrombotic thrombocytopenic purpura of long duration. Am. J. Med., *27:* 333, 1959.
36. Cameron, J. S. and Vick, R.: Plasma C-3 in haemolytic-uraemic syndrome and thrombotic thrombocytopenic purpura. Letter. Lancet, *2:* 975, 1973.
37. Casale, L. A.: Thrombotic thrombocytopenic purpura: Report of a case and review of 157 cases. Hawaii Med. J., *25:* 93, 1965.
38. Case Records of the Massachusetts General Hospital. N. Engl. J. Med., *272:* 963, 1965.
39. Case Records of the Massachusetts General Hospital. N. Engl. J. Med., *275:* 1125, 1966.
40. Case Records of the Massachusetts General Hospital. N. Engl. J. Med., *278:* 36, 1968.
41. Case Records of the Massachusetts General Hospital. N. Engl. J. Med., *278:* 1336, 1968.
42. Case Records of the Massachusetts General Hospital. N. Engl. J. Med., *300:* 1097, 1979.
43. Celada, A. and Perrin, L. H.: Circulating immune complexes in thrombotic thrombocytopenic purpura (TTP). Letter. Blood, *52:* 855, 1978.
44. Chung, E. B. and Gomez-Acebo, J.: Thrombotic thrombocytopenic purpura: A report of two cases with some unusual features. Georgetown Med. Bull., *14:* 137, 1960.
45. Clinicopathologic Conference. New York State J. Med., *67:* 702, 1967.
46. Clinicopathologic Conference. J. Pediatr., *73:* 788, 1968.
47. CPC (Clinicopathologic Conference). Am. J. Med., *68:* 267, 1980.
48. CPC (Clinicopathologic Conference). Am. J. Med., *63:* 789, 1977.
49. Cocchetto, D. M., Cook, L., Cato, A. E., Niedel, J. E.: Rationale and proposal for use of prostacyclin in thrombotic thrombocytopenic purpura therapy. Semin. Thromb. Hemostasis, *7:* 43, 1981.
50. Couch, W. D.: Giant lymph node hyperplasia associated with thrombotic thrombocytopenic purpura. Am. J. Clin. Pathol., *74:* 340, 1980.
51. Cox, E. C.: Thrombotic thrombocytopenic purpura: Report of three additional cases and a short review of the literature. J. S. Carolina Med. Assoc., *62:* 465, 1966.
52. Craig, J. M. and Gitlin, D.: The nature of the hyaline thrombi in the thrombotic thrombocytopenic purpura. Am. J. Pathol., *33:* 251, 1957.
53. Cuttner, J.: Splenectomy, steroids and dextran 70 in thrombotic thrombocytopenic purpura. J.A.M.A., *227:* 397, 1974.
54. Cuttner, J.: Thrombotic thrombocytopenic purpura: A ten-year experience. Blood, *56:* 302, 1980.
55. Dekker, A., O'Brien, M. E. and Cammarata, R. J.: The association of thrombotic thrombocytopenic purpura with systemic lupus erythematosus. Am. J. Med. Sci., *267:* 243, 1974.
56. Denel, T., Gardner, F., Peck, W. A. and Avioli, L. V.: Thrombotic thrombocytopenic purpura. Arch. Intern. Med., *140:* 93, 1980.
57. DeSaussure, C.: Thrombotic thrombocytopenic purpura. A case report. J. S. Carolina Med. Assoc., *60:* 320, 1964.
58. Distenfeld, A. and Oppenheim, E.: The treatment of acute thrombotic thrombocytopenic purpura with corticosteroids and splenectomy. Report of three cases. Ann. Intern. Med., *65:* 245, 1966.
59. Dunea, G., Muehrcke, R. C., Nakamoto, S. and Schwartz, F. D.: Thrombotic thrombocytopenic purpura with acute anuric renal failure. Amer. J. Med., *41:* 1000, 1966.
60. Eckel, R. H., Crowell, E. B., Waterhouse, B. E. and Bozdech, M. J.: Platelet-inhibiting drugs in thrombotic thrombocytopenic purpura. Arch. Intern. Med., *137:* 735, 1977.
61. Ekberg, M., Nilsson, I. M. and Denneberg, T.: Coagulation studies in hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Acta. Med. Scand., *196:* 373, 1974.
62. Fagiolo, E.: Thrombotic thrombocytopenic purpura with autoimmune pancytopenia. Acta. Haematol., *52:* 356, 1974.
63. Faguet, G. B. and King, M. B.: Thrombotic thrombocytopenic purpura: Treatment with antiplatelet agents. Am. J. Med. Sci., *268:* 113, 1974.
64. Feldman, J. D., Mardincy, M. R., Unanue, E. R. and Cutting, H.: The vascular pathology of thrombotic thrombocytopenic purpura. Lab. Invest., *15:* 927, 1966.
65. Fiddes, P. J. and Penny, R.: Fibrin degradation products in thrombotic thrombocytopenic purpura. Aust. Ann. Med., *4:* 350, 1970.
66. Fisher, W. B.: Exchange transfusion in acute thrombotic thrombocytopenic purpura: Case report. Milit. Med., *142:* 789, 1977.
67. Fox, P. C., Gordon, R. E. and Williams, A. C.: Thrombotic thrombocytopenic purpura: Report of a case. J. Oral. Surg., *35:* 921, 1977.
68. Fuchs, W. E., George, J. N., Dotin, L. N. and Sears, D. A.: Thrombotic thrombocytopenic purpura. Occurrence two years apart during late pregnancy in two sisters. J.A.M.A., *235:* 2126, 1976.
69. Geisinger, K. R. and Solomon, A. R.: Sudden cardiac death in thrombotic thrombocytopenic purpura. Letter. Arch. Pathol. Lab. Med., *103:* 599, 1979.
70. Girounini, M., Bouvier, C. A., Dami, R., Denizot, M. and Jannet, M.: Effect of dipyridamole and aspirin in thrombotic microangiopathy. Br. Med. J., *1:* 545, 1972.
71. Gitlin, D. and Craig, J. M.: Variations in the staining characteristics of human fibrin. Am. J. Pathol., *33:* 267, 1957.
72. Goldenfarb, P. B. and Finch, S. C.: Thrombotic thrombocytopenic purpura. A ten-year survey. J.A.M.A., *226:* 644, 1973.
73. Goodman, A., Ramos, R., Petrelli, M., Hirsch, S. A., Bukowski, R. and Harris, J. W.: Gingival biopsy in thrombotic thrombocytopenic purpura. Ann. Intern. Med., *89:* 501, 1978.
74. Goodman, G.: Thrombotic thrombocytopenic purpura. Ariz. Med., *37:* 180, 1980.
75. Gore, I.: Disseminated arteriolar and capillary platelet thrombosis. A morphologic study of its histogenesis. Am. J. Pathol., *26:* 155,

1950.
76. Gottschall, J. L., Pisciotta, A. V., Darin, J., Hussey, C. V., and Aster, R. H.: Thrombotic thrombocytopenic purpura: Experience with whole blood exchange transfusion. Semin. Thromb. Hemostasis, *7:* 25, 1981.
77. Gruenewald, R. L. and Perry, M. C.: Thrombotic thrombocytopenic purpura. Missouri Med., *76:* 316, 1979.
78. Gundlach, W. J. and Tarnasky, R.: Thrombotic thrombocytopenic purpura. Remission following therapy with aspirin and dipyridamole. Minn. Med., *60:* 20, 1977.
79. Hanzlick, R. L., Shah, N. T. and Senhauser, D. A.: Treatments for thrombotic thrombocytopenic purpura: Plasma, vincristine, hemodialysis and exchange transfusion. Letter. N. Engl. J. Med., *298:* 971, 1978.
80. Harker, L. A. and Slichter, S. J.: Platelet and fibrinogen consumption in man. N. Engl. J. Med., *287:* 999, 1972.
81. Harrison, E. E. and Hickman, J. W.: Hemolytic anemia and thrombocytopenia associated with penicillamine ingestion. South Med. J., *68:* 113, 1975.
82. Hellman, R. M., Jackson, D. V. and Buss, D. H.: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in HLA-identical siblings. Ann. Intern. Med., *93:* 282, 1980.
83. Hill, J. B. and Cooper, W. M.: Thrombotic thrombocytopenic purpura: Treatment with corticosteroids and splenectomy. Arch. Intern. Med., *122:* 353, 1968.
84. Howard, D. J., Roberts, A. B. and Page, F. T.: Late recurrence of TTP after splenectomy. Br. Med. J., *2:* 319, 1975.
85. Howard, T. P.: Fulminant respiratory failure. A manifestation of thrombotic thrombocytopenic purpura. J.A.M.A., *242:* 350, 1979.
86. Jaffe, E. A., Nachman, R. L. and Merskey, C.: Thrombotic thrombocytopenic purpura-coagulation parameters in 12 patients. Blood, *42:* 499, 1973.
87. James, T. N. and Monto, R. W.: Pathology of the cardiac conduction system in thrombotic thrombocytopenic purpura. Ann. Intern. Med., *65:* 37, 1966.
88. Jobin, F. and Delage, J. M.: Aspirin and prednisone in microangiopathic haemolytic anaemia. Letter. Lancet., *2:* 208, 1970.
89. Kadri, A., Moinuddin, M. and Leeuw, N. K. M.: Phagocytosis of blood cells by splenic macrophages in thrombotic thrombocytopenic purpura. Ann. Intern. Med., *82:* 799, 1975.
90. Kaplan, B. S. and Drummond, K. N.: The hemolytic uremic syndrome is a syndrome. N. Engl. J. Med., *298:* 964, 1978.
91. Kass, L.: Nuclear "speckling" in thrombotic thrombocytopenic purpura proerythroblasts. Am. J. Clin. Pathol., *59:* 869, 1973.
92. Kass, L.: Megakaryocytic abnormalities in thrombotic thrombocytopenic purpura. Am. J. Clin. Pathol., *61:* 639, 1974.
93. Kennedy, A.: Thrombotic thrombocytopenic purpura. Letter. Canad. Med. Assoc. J., *90:* 450, 1964.
94. Kennedy, S. S., Zacharski, L. R., Beck, J. R.: Thrombotic thrombocytopenic purpura: Analysis of 48 unselected cases. Semin. Thromb. Hemostasis, *6:* 341, 1980.
95. Kutell, M. A., Alfrey, C. P. and Hettig, R. A.: Thrombotic thrombocytopenic purpura. Therapy. Letter. N. Engl. J. Med., *285:* 971, 1971.
96. Kwann, H. C.: The pathogenesis of thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *5:* 184, 1979.
97. Kwann, H. C.: Role of fibrinolysis in thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *6:* 395, 1980.
98. Lerner, R. G., Rapaport, S. J. and Meltzer, J.: Thrombotic thrombocytopenic purpura. Serial clotting studies, relation to the generalized Shwartzman reaction, and remission after adrenal steroid and dextran therapy. Ann. Intern. Med., *66:* 1180, 1967.
99. Levin, H. and Alfrey, C. P.: Thrombotic thrombocytopenic purpura: Temporary remission induced by prednisone. Texas Med., *62:* 72, 1966.
100. Levine, S. and Shearn, M. A.: Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. Arch. Intern. Med., *113:* 826, 1964.
101. Lewellen, D. R. Jr. and Singerman, L. J.: Thrombotic thrombocytopenic purpura with optic disk neovascularization, vitreous hemorrhage, retinal detachment and optic atrophy. Am. J. Ophthalmol., *89:* 840, 1980.
102. Lian, E. C. Y.: The role of increased platelet aggregation in TTP. Semin. Thromb. Hemostasis, *6:* 401, 1980.
103. Lian, E. C. Y., Harkness, D. R., Byrnes, J. J., Wallach, H. and Nunez, R.: Presence of a platelet aggregating factor in the plasma of patients with thrombotic thrombocytopenic purpura (TTP) and its inhibition by normal plasma. Blood, *53:* 333, 1979.
104. Lukes, R. J., Rath, C. E., Steussy, C. N. and Mailliard, J.: Thrombotic thrombocytopenic purpura: Clinical and pathologic findings in 49 cases (Abstr.) Proc. Amer. Soc. Hemat. Montreal, 1960. Blood, *17:* 366, 1961.
105. Lynch, E. C., Sharp, J. T., Freel, H. L., Helgason, A. H. and Dorrson, R. E.: Clinicopathologic Conference. Texas Med., *64:* 69, 1968.
106. MacIntyre, D. E., Pearson, J. D. and Gordon, J. L.: Localization and stimulation of prostacyclin production in vascular cells. Nature, *271:* 549, 1978.
107. Mant, M. J., Cauchi, M. N. and Medley, G.: Thrombotic thrombocytopenic purpura: Report of a case with possible immune etiology. Blood, *40:* 416, 1972.
108. Marmont, A. M.: Thrombotic thrombocytopenic purpura successfully treated with a combination of dipyridamole and aspirin. Haematologica (Pavin), *65:* 222, 1980.
109. Mars, D. R.: Thrombotic thrombocytopenic purpura after a dogbite. South. Med. J., *73:* 676, 1980.
110. May, H. V., Harbert, G. M. and Thornton, W. N.: Thrombotic thrombocytopenic purpura associated with pregnancy. Am. J. Obstet. Gynecol., *126:* 452, 1976.
111. McCutcheon, S. A., Rupe, C. E., Barnhart, M. I. and Fine, G.: A case of renal thrombotic thrombocytopenic purpura. Henry Ford Hosp. Med. J., *16:* 239, 1968.
112. McLeod, B. C., Wu, K. K. and Knopse, W. H.: Plasmapheresis in thrombotic thrombocytopenic purpura. Arch. Intern. Med., *140:* 1059, 1980.
113. Medd, W. L. and Sodhi, H. S.: Therapy for thrombotic thrombocytopenic purpura. Ann. Intern. Med., *86:* 658, 1977.
114. Meister, R. J., Sacher, R. A. and Philips, T.: Immune complexes in thrombotic thrombocytopenic purpura. Letter. Ann. Intern. Med., *90:* 717, 1978.
115. Mettler, N. E.: Isolation of a microtatobiote from patients with hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and from mites in the United States. N. Engl. J. Med., *281:* 1023, 1969.
116. Miller, W. M., Stass, S. A. and Schumacher, H. R.: Lymph node biopsy in thrombotic thrombocytopenic purpura. Letter. Ann. Intern. Med., *90:* 278, 1978.
117. Mitch, W. E., Spivak, J. L., Spangler, D. B. and Bell, W. R.: Thrombotic thrombocytopenic purpura presenting with gynaecological manifestations. Lancet, *1:* 849, 1973.
118. Monahan, L. K.: A review of thrombotic thrombocytopenic purpura. J. Kansas Med. Soc., *70:* 244, 1969.
119. Moncada, S., Higgs, E. A. and Vane, J. R.: Human arterial and venous tissues generate prostacyclin (prostaglandin X), a potent inhibitor of platelet aggregation. Lancet, *1:* 18, 1977.
120. Monnens, L. A. and Retera, R. J. M.: Thrombotic thrombocytopenic purpura in a neonatal infant. J. Pediat., *71:* 118, 1967.
121. Monroe, W. M. and Strauss, H. A. F.: Intravascular hemolysis: A morphologic study of schizocytes in thrombotic purpura and other diseases. Southern Med. J., *46:* 837, 1953.
122. Moon, E. C. and Kitay, D. Z.: Hematologic problems in pregnancy: II. Thrombotic (thrombohemolytic) thrombocytopenic purpura. J. Reprod. Med., *9:* 212, 1972.
123. Moorhead, J. F.: Thrombotic thrombocytopenic purpura. Recovery after splenectomy. Arch. Intern. Med., *117:* 284, 1966.
124. Morrison, J. and McMillan, R.: Elevated platelet-associated IgG in thrombotic thrombocytopenic purpura. J.A.M.A., *238:* 1944, 1977.
125. Moschcowitz, E.: An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries. Arch. Intern. Med., *31:* 89, 1925.
126. Myers, T. J.: Treatment of thrombotic thrombocytopenic purpura with combined exchange plasmapheresis and anti-platelet agents. Semin. Thromb. Hemostasis, *7:* 37, 1981.
127. Myers, T. J., Wakem, C. J., Ball, E. D. and Tremont, S. J.: Thrombotic thrombocytopenic purpura: Combined treatment with plasmapheresis and anti-platelet agents. Ann. Intern. Med., *92:* 149, 1980.
128. Nalbandian, R. M.: Thrombotic thrombocytopenic purpura. An extended editorial. Semin. Thromb. Hemostasis, *5:* 216, 1979.
129. Nalbandian, R. M., Henry, R. L.: A proposed comprehensive pathophysiology of thrombotic thrombocytopenic purpura with implicit novel tests and therapies. Semin. Thromb. Hemostasis, *6:* 356, 1980.
130. Nally, J. V. and Metz, E. N.: Acute thrombotic thrombocytopenic purpura. Another cause for hemolytic anemia and thrombocytopenia in cirrhosis. Arch. Intern. Med., *139:* 711, 1979.
131. Neame, P. B.: Immunologic and other factors in thrombotic thrombocytopenic purpura (TTP). Semin. Thromb. Hemostasis, *6:* 416, 1980.
132. Neame, P. B., Lechago, J., Ling, E. T. and Koval, A.: Thrombotic thrombocytopenic purpura: Report of a case with disseminated intravascular platelet aggregation. Blood, *42:* 805, 1973.

133. Neame, P. B., Hirsh, J., Browman, G., Denburg, J., D'Souza, T. J., Gallus, A. and Brain, M. C.: Thrombotic thrombocytopenic purpura: A syndrome of intravascular platelet consumption. Can. Med. Assoc. J., *114:* 1108, 1976.
134. Neame, P. B. and Hirsh, J.: Circulating immune complexes in thrombotic thrombocytopenic purpura (TTP). Letter. Blood, *51:* 559, 1978.
135. Norkin, S. A., Freedman, H. H. and Evans, G. W.: Thrombotic thrombocytopenic purpura in siblings. Am. J. Med., *43:* 294, 1967.
136. Okuno, T.: Plasmapheresis for thrombocytopenia. Letter. Lancet, *1:* 1095, 1978.
137. Okuno, T. and Kosova, L.: Plasmapheresis for thrombotic thrombocytopenic purpura (TTP). Transfusion, *19:* 342, 1979.
138. Olsen, H.: Thrombotic thrombocytopenic purpura as a cause of pancreatitis. Digest Dis., *18:* 238, 1973.
139. Orbison, J. L.: Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms. Am. J. Pathol., *27:* 129, 1951.
140. Parker, J. C. and Barrett, D. A. II: Microangiopathic hemolysis and thrombocytopenia related to penicillin drugs. Arch. Intern. Med., *127:* 474, 1971.
141. Paz, R. A., Elijovich, F., Barent, J. A. and Sanchez-Avalos, J. C.: Fatal simultaneous thrombocytopenic purpura in siblings. Br. Med. J., *4:* 727, 1969.
142. Penny, R.: Thrombocytopenic purpura. Med. J. Austral., *1:* 767, 1965.
143. Percival, S. P. B.: The eye and Moschcowitz's disease. A review of 182 cases. Trans. Ophth. Soc. U.K., *90:* 375, 1970.
144. Perel, I. D. and Forgan-Smith, W. R.: Thrombotic thrombocytopenic purpura presenting as eclampsia. Aust. N.Z. J. Obstet. Gynaecol., *12:* 257, 1972.
145. Peterson, J., Amarc, M., Henry, J. E. and Bone, R. C.: Splenectomy and antiplatelet agents in thrombotic thrombocytopenic purpura. Am. J. Med. Sci., *277:* 75, 1979.
146. Petitt, R. M.: Thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *6:* 350, 1980.
147. Petz, L. D.: Neurological manifestations of systemic lupus erythematosus and thrombotic thrombocytopenic purpura. Stroke, *8:* 719, 1977.
148. Pilz, P.: Moschcowitz syndrome with involvement of the central nervous system. Virchows Arch. Path. Histol. (Path. Anat.), *366:* 59, 1975.
149. Pisciotta, A. V.: Thrombotic thrombocytopenic purpura. Ann. Intern. Med., *92:* 249, 1980.
150. Pisciotta, A. V., Garthwaite, T., Darin, J. and Aster, R. H.: Treatment of thrombotic thrombocytopenic purpura by exchange transfusion. Am. J. Hematol., *3:* 73, 1977.
151. Pisciotta, A. V., Gottschall, J. L.: Clinical features of thrombotic thrombocytopenic purpura. Semin. Thromb. Hemostasis, *6:* 330, 1980.
152. Piver, M. S., Lisker, S. A., Rowan, N., Weber, L., Brody, J. I. and Beizer, L. H.: Thrombotic thrombocytopenic purpura during pregnancy. Am. J. Obstet. Gynecol., *100:* 302, 1968.
153. Ramkissoon, R. A.: Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. Calif. Med., *104:* 212, 1966.
154. Rankin, W. E., Hart, M. N. and Weisenburger, D. D.: Thrombotic thrombocytopenic purpura in a child with Alexander's disease. Arch. Path. Lab. Med., *101:* 655, 1977.
155. Reiss, R., Shah, V., Kalter, R. and Panlilio, A.: Plasmapheresis in thrombotic thrombocytopenic purpura (TTP). Letter. Blood, *51:* 560, 1978.
156. Remuzzi, G., Cavenaghi, A. E., Mecca, G., Donati, M. B. and Gaetano, G. de: Prostacyclin-like activity and bleeding in renal failure. Lancet, *2:* 1195, 1977.
157. Remuzzi, G., Misiani, R., Mecca, G., Gaetano, G. and Donati, M. B.: Thrombotic thrombocytopenic purpura—a deficiency of plasma factors regulating platelet-vessel-wall interaction? Letter. N. Engl. J. Med., *299:* 311, 1978.
158. Remuzzi, G., Rossi, E. C., Misiani, R., Marchesi, D., Mecca, G., de Gaetano, G., Donati, M. B.: Prostacyclin and thrombotic microangiopathy. Semin. Thromb. Hemostasis, *6:* 391, 1980.
159. Rennard, S. and Abe, S.: Decreased cold-insoluble globulin in congenital thrombocytopenia (Upshaw-Schulman syndrome). Letter. N. Engl. J. Med., *300:* 368, 1979.
160. Reynolds, P. M., Jackson, J. M., Brine, J. A. S. and Vivian, A. B.: Thrombotic thrombocytopenic purpura—remission following splenectomy. Am. J. Med., *61:* 439, 1976.
161. Richardson, J. H. and Smith, B. T.: Thrombotic thrombocytopenic purpura. Survival in pregnancy with heparin sodium therapy. J.A.M.A., *203:* 176, 1968.
162. Richmond, J. M., d'Apice, A. J. F., Whitworth, T. A. and Kincaid-Smith, P.: Thrombotic thrombocytopenic purpura and anuria: Response to plasma exchange. Aust. N.Z. J. Med., *10:* 48, 1980.
163. Ridolfi, R. L., Hutchins, G. M. and Bell, W. R.: The heart and conduction system in thrombotic thrombocytopenic purpura. Ann. Intern. Med., *91:* 357, 1979.
164. Rivero, L. and Ritz, N. D.: Abnormal fibrinogen in thrombotic thrombocytopenic purpura. Blood, *32:* 140, 1968.
165. Robboy, S. J., Colman, R. W. and Minna, J. D.: Pathology of disseminated intravascular coagulation (DIC). Human Pathol., *3:* 327, 1972.
166. Rossi, E. C., Del Greco, F.: The adaptation of hemodialysis to facilitate rapid exchange transfusion in patients with thrombotic thrombocytopenic purpura (TTP). Semin. Thromb. Hemostasis, *7:* 22, 1981.
167. Rossi, E. C., Redondo, D. and Borges, W. H.: Thrombotic thrombocytopenic purpura. Survival following treatment with aspirin, dipyridamole and prednisone. J.A.M.A., *228:* 1141, 1974.
168. Rubinstein, M. A., Kagan, B. M., MacGillviray, M. H., Merliss, R. and Sacks, H.: Unusual remission in a case of thrombotic thrombocytopenic purpura syndrome following fresh blood exchange transfusions. Ann. Intern. Med., *51:* 1409, 1959.
169. Ruffolo, E. H., Pease, G. L. and Cooper, T.: Thrombotic thrombocytopenic purpura. Arch. Intern. Med., *110:* 78, 1962.
170. Rutkow, I. M.: Thrombotic thrombocytopenic purpura (TTP) and splenectomy. Ann. Surg., *188:* 701, 1978.
171. Ryan, P. F. J., Cooper, I. A. and Firkin, B. G.: Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. Med. J. Austral., *1:* 69, 1979.
172. Scharoff, J. R., Serlin, N. and Atamer, M. A.: Thrombotic thrombocytopenic purpura. Report of a case treated with splenectomy and steroids. Acta. Haematol., *41:* 180, 1969.
173. Schuette, P. T., Brabham, A. M. and Eurenius, K.: Thrombotic thrombocytopenic purpura—a re-evaluation. South Med. J., *67:* 915, 1974.
174. Schwartz, J., Rosenberg, A. and Cooperberg, A. A.: Thrombotic thrombocytopenic purpura: Successful treatment of two cases. Canad. Med. Assoc. J., *106:* 1200, 1972.
175. Schwartz, M. L. and Brenner, W. E.: The obfuscation of eclampsia by thrombotic thrombocytopenic purpura. Am. J. Obstet. Gynec., *131:* 18, 1978.
176. Shapiro, D. M., Zeluff, G. W., Wilson, K., Natelsen, E. A. and Lynch, E. C.: Thrombotic thrombocytopenic purpura occurring despite absence of spleen: Report of a case. J. Am. Osteopath. Assoc., *75:* 798, 1976.
177. Silverstein, A.: Concerning the initial neurologic manifestations of thrombotic thrombocytopenic purpura. Trans. Amer. Neur. Assoc., *92:* 112, 1967.
178. Silverstein, A.: Thrombotic thrombocytopenic purpura. The initial neurologic manifestations. Arch. Neurol., *18:* 358, 1968.
179. Simpfendorfer, C. C.: Therapy for thrombotic thrombocytopenic purpura. Letter. Ann. Intern. Med., *86:* 657, 1977.
180. Singer, K.: Thrombotic thrombocytopenic purpura. Adv. Intern. Med., *6:* 195, 1954.
181. Steinberg, A. D., Green, W. T. and Talal, N.: Thrombotic thrombocytopenic purpura complicating Sjogren's syndrome. J.A.M.A., *215:* 757, 1971.
182. Stern, R., Cornell, C. J., Beck, R. and Smith, R. E.: Thrombotic thrombocytopenic purpura: Failure of plasma infusion and antiplatelet agents. Letter. Ann. Intern. Med., *90:* 989, 1978.
183. Stoever, W. W., Staab, R. C. and Fogel, R. M.: Thrombotic thrombocytopenic purpura. J. A.O.A., *66:* 519, 1967.
184. Stonesifer, L. D., Bone, R. C. and Hiller, F. C.: Thrombotic thrombocytopenic purpura in carbon monoxide poisoning. Arch. Intern. Med., *140:* 104, 1980.
185. Taft, E. G.: Thrombotic thrombocytopenic purpura and dose of plasma exchange. Blood, *54:* 842, 1979.
186. Taft, E. G., Baldwin, S. T.: Plasma exchange transfusion. Semin. Thromb. Hemostasis, *7:* 15, 1981.
187. Tapp, E., Geary, C. G. and Dawson, D. W.: Thrombotic microangiopathy with macroscopic infarction. J. Pathol., *97:* 711, 1969.
188. Tartaglia, A. P. and Burkart, P. T.: Thrombotic thrombocytopenic purpura. Remission following hemodialysis. J.A.M.A., *218:* 999, 1971.
189. Umlas, J.: Glomeruloid structures in thrombohemolytic thrombocytopenic purpura, glomerulonephritis and disseminated intravascular coagulation. Hum. Pathol., *3:* 437, 1972.
190. Umlas, J. and Kaiser, J.: Thrombohemolytic thrombocytopenic purpura (TTP). A disease or syndrome? Amer. J. Med., *49:* 723, 1970.
191. Updike, S. J., Bozdech, M. J., Johnson, C. A., Zimmerman, S. W.: Management of fulminating thrombotic thrombocytopenic purpura.

Semin. Thromb. Hemostasis, *7:* 33, 1981.
192. Upshaw, J. D., Jr.: Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. N. Engl. J. Med., *298:* 1350, 1978.
193. Vanderwalle, A., Kanfer, A. and Kourilsky, O.: Oliguric thrombotic microangiopathy during the fifth month of pregnancy. Br. Med. J., *2:* 479, 1975.
194. Van Slyck, E. J., Jurgensen, J. C. and Cargill, J. W.: Diabetes insipidus complicating thrombotic thrombocytopenic purpura. J.A.M.A., *209:* 768, 1969.
195. Vesconi, S.: Thrombotic thrombocytopenic purpura during oral contraceptive therapy. Letter. Thromb. Hemostasis, *40:* 563, 1978.
196. Vilanova, J. R., Norenberg, M. D. and Stuard, I. D.: Thrombotic thrombocytopenic purpura. Systemic embolization from nonbacterial thrombotic endocarditis. N.Y. State J. Med., *75:* 2246, 1975.
197. Walker, B. K., Ballas, S. K. and Martinez, J.: Plasma infusion for thrombotic thrombocytopenic purpura during pregnancy. Arch. Intern. Med., *140:* 981, 1980.
198. Wallace, D. C., Lovric, A., Clubb, J. S. and Carseldine, D. B.: Thrombotic thrombocytopenic purpura in four siblings. Am. J. Med., *58:* 724, 1975.
199. Watson, C. G. and Cooper, W. M.: Thrombotic thrombocytopenic purpura. Concomitant occurrence in husband and wife. J.A.M.A., *215:* 1821, 1971.
200. Weisenburger, D. D., O'Conner, M. L. and Hart, M. N.: Thrombotic thrombocytopenic purpura with C'3 vascular deposits. Am. J. Clin. Pathol., *67:* 61, 1979.
201. Woodruff, R. K. and Castaldi, P. A.: Treatment of TTP with high-dose dipyridamole. Letter. Blood., *52:* 856, 1978.
202. Wurzel, J. M.: TTP lesions in placenta but not fetus. Letter. N. Engl. J. Med., *301:* 503, 1979.
203. Yang, C., Nussbaum, M. and Park, H.: Thrombotic thrombocytopenic purpura in early pregnancy. Acta. Haematol., *62:* 112, 1979.
204. Yudis, M., Reid, J., Burd, R. and Millerick, J.: Septic abortion masquerading as thrombotic thrombocytopenic purpura. Am. J. Obstet. Gynecol., *111:* 350, 1971.
205. Zacharski, L. R., Walworth, C. and McIntyre, O. R.: Antiplatelet therapy for thrombotic thrombocytopenic purpura. Letter. N. Engl. J. Med., *285:* 408, 1971.
206. Zacharski, L. R., Lusted, D. and Glick, J. L.: Thrombotic thrombocytopenic purpura in a previously splenectomized patient. Am. J. Med., *60:* 1061, 1976.
207. Zeluff, G. W., Natelson, E. A. and Jackson, D.: Thrombocytopenic purpura—Idiopathic and thrombotic. Heart and Lung, *7:* 327, 1978.

U.S. POSTAL SERVICE

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

(Required by 39 U.S.C. 3685)

1. TITLE OF PUBLICATION	A. PUBLICATION NO	2. DATE OF FILING
Medicine	0 0 2 5 7 9 7 4	10/1/81
3. FREQUENCY OF ISSUE	A. NO. OF ISSUES PUBLISHED ANNUALLY	B. ANNUAL SUBSCRIPTION PRICE
Bi-monthly	6	$25.00

4. COMPLETE MAILING ADDRESS OF KNOWN OFFICE OF PUBLICATION *(Street, City, County, State and ZIP Code) (Not printers)*

428 East Preston Street, Baltimore, Maryland 21202

5. COMPLETE MAILING ADDRESS OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS *(Not printers)*

428 East Preston Street, Baltimore, Maryland 21202

6. FULL NAMES AND COMPLETE MAILING ADDRESS OF PUBLISHER, EDITOR, AND MANAGING EDITOR *(This item MUST NOT be blank)*

PUBLISHER *(Name and Complete Mailing Address)*

Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202

EDITOR *(Name and Complete Mailing Address)*

A. McGehee Harvey, M.D., Johns Hopkins Hospital, Balto., MD 21205

MANAGING EDITOR *(Name and Complete Mailing Address)*

7. OWNER *(If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated.) (Item must be completed)*

FULL NAME	COMPLETE MAILING ADDRESS
Waverly Press, Inc.	Mt. Royal & Guilford Aves. Baltimore, MD 21202

8. KNOWN BONDHOLDERS, MORTGAGEES, AND OTHER SECURITY HOLDERS OWNING OR HOLDING 1 PERCENT OR MORE OF TOTAL AMOUNT OF BONDS, MORTGAGES OR OTHER SECURITIES *(If there are none, so state)*

FULL NAME	COMPLETE MAILING ADDRESS
None	

9. FOR COMPLETION BY NONPROFIT ORGANIZATIONS AUTHORIZED TO MAIL AT SPECIAL RATES *(Section 411.3, DMM only)*
The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes *(Check one)*

☒ (1) HAS NOT CHANGED DURING PRECEDING 12 MONTHS ☐ (2) HAS CHANGED DURING PRECEDING 12 MONTHS *(If changed, publisher must submit explanation of change with this statement.)*

10. EXTENT AND NATURE OF CIRCULATION	AVERAGE NO. COPIES EACH ISSUE DURING PRECEDING 12 MONTHS	ACTUAL NO. COPIES OF SINGLE ISSUE PUBLISHED NEAREST TO FILING DATE
A. TOTAL NO. COPIES *(Net Press Run)*	11143	10435
B. PAID CIRCULATION 1. SALES THROUGH DEALERS AND CARRIERS, STREET VENDORS AND COUNTER SALES	None	None
2. MAIL SUBSCRIPTION	8823	8928
C. TOTAL PAID CIRCULATION *(Sum of 10B1 and 10B2)*	8823	8928
D. FREE DISTRIBUTION BY MAIL, CARRIER OR OTHER MEANS SAMPLES, COMPLIMENTARY, AND OTHER FREE COPIES	78	72
E. TOTAL DISTRIBUTION *(Sum of C and D)*	8901	9000
F. COPIES NOT DISTRIBUTED 1. OFFICE USE, LEFT OVER, UNACCOUNTED, SPOILED AFTER PRINTING	2242	1435
2. RETURN FROM NEWS AGENTS	None	None
G. TOTAL *(Sum of E, F1 and 2 - should equal net press run shown in A)*	11143	10435

11. I certify that the statements made by me above are correct and complete

SIGNATURE AND TITLE OF EDITOR, PUBLISHER, BUSINESS MANAGER, OR OWNER: Publisher

PS Form June 1980 3526 (Page 1) *(See instruction on reverse)*