Thrombotic Thrombocytopenic Purpura in Childhood

By James B. MacWhinney, Jr., James T. Packer, Gerald Miller, and Robert M. Greendyke

Thrombotic thrombocytopenic purpura (TTP) is a disease of unknown etiology which has as its most characteristic morphologic feature multiple hyaline thrombi. The clinical manifestations of the disease are hemolytic anemia, purpura, thrombocytopenia, fever, and signs and symptoms of neurologic dysfunction. While the course of the illness is usually measured in weeks, in some cases the process extends over a period of several years.

We will describe two unusual cases of TTP in children; based on studies of these two patients and a review of the literature of TTP in childhood, we will emphasize certain clinical and pathologic features of this disorder.

Case 1 (S. I.) (SMH Unit No. 35-48-37)

This 13-year-old white girl died after an illness of 12 years which was characterized by recurring episodes of hemolytic anemia, thrombocytopenia, and renal disease. Shumway and Miller described the course and nature of this girl’s illness during the first 9½ years of her life. They emphasized the fact that exacerbations of anemia were associated with bizarre red cell morphology and that the hemolytic mechanism was extracorpuscular in nature. The patient’s illness continued to be episodic until age 13 when she entered a chronic state characterized by laboratory evidence of anemia and renal disease. This chronic phase was brought to an end by a terminal phase of a few days’ duration.

The details are given in the appendix.

Special Hematologic Studies—Case 1 (made during last three months of life)

1. Erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) activity was increased to 191 U./100 ml. RBC (normal mean value 113 U./100 ml. RBC, range of normal is 70–140 U./100 ml. RBC).

2. Heinz body test. No Heinz bodies were seen until the patient’s erythrocytes were incubated with acetylphenylhydrazine when over 90 per cent of the cells were seen to have five or more Heinz bodies. In the normal control sample, less than 15 per cent of the erythrocytes had five or more Heinz bodies.

3. Family studies: Erythrocytes from the patient’s mother, father, and two sisters had normal G-6-PD activity, and the cells behaved normally in the Heinz body test.

4. The patient’s serum and normal serum were incubated with normal erythrocytes and erythrocytes from a patient sensitive to fava beans (G-6-PD deficiency). After incubation at 37 C. for five hours, the red blood cells were examined for morphology, Heinz bodies, and content of reduced glutathione.

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(GSH). Under these conditions the normal control serum and the patient’s serum were comparable in causing no change in GSH content, no change in erythrocyte morphology, and in failing to produce Heinz bodies.

(5) Spectrophotometric analysis of the patient’s hemoglobin revealed no abnormality.

Autopsy Findings (A-19010)

At autopsy, the body was that of a well developed, thin white female of 13 years. There were no petechiae on the skin although a 0.5 x 1 cm. ecchymosis was present in the upper outer quadrant of the right bulbar conjunctiva. A 10 cm. well-healed paramedian incisional scar was present in the left upper quadrant of the abdomen at the site of the previous splenectomy.

Numerous small ecchymoses were present in the epicardial and endocardial surfaces of both ventricles. No lesions were grossly evident within the myocardium. Small ecchymoses were scattered over the surfaces of both lungs, visible just beneath the visceral pleura. Sectioning of the lungs revealed dark red to gray, elevated, granular, poorly circumscribed, 0.5-1 cm. nodular areas of increased density in both lower lobes which tended to be localized near bronchi. The spleen was absent.

The kidneys weighed 130 and 110 Gm. The capsules stripped easily from mottled yellowish brown, smooth surfaces. A few scattered petechiae were noted. The sectioned cortex was 5 mm. thick, with indistinct striations. Scattered glomeruli appeared more prominent than usual. Fresh hemorrhage surrounded several of the papillae.

The brain weighed 1430 Gm. and was edematous. After fixation in 10 per cent formalin, the lateral surface of the right frontal cortex was soft and granular.

Microscopically, focal areas of coagulation necrosis were present in myocardium, right cerebral cortex, adrenal, and liver. Associated with these foci of necrosis were vascular lesions which involved small arteries and arterioles. Many of the involved vessels contained acellular, homogeneous to finely granular, eosinophilic, hyaline masses which partially or completely occluded the vascular lumina. Marked endothelial hyperplasia was present in some arterioles, but none of the vascular lesions was associated with a cellular exudate.

Scattered throughout both lungs were areas of acute inflammatory exudate, which was both intra-alveolar and interstitial in location. The inflammatory exudate tended to be localized around bronchi and bronchioles but was confluent in some areas.

The kidneys showed marked histologic changes. Some glomeruli were hypercellular, and many appeared devoid of red blood cells. Basement membranes appeared thickened focally. Fusion of glomerular capillary tufts and adhesions between Bowman’s capsule and glomeruli were apparent. A rare glomerulus showed almost complete hyalination.

A striking, and in our experience unique, proliferation of endothelial cells was present at the vascular pole of many glomeruli (fig. 4). These spindle-shaped cells with pale cytoplasm permeated the area usually occupied by the juxtaglomerular arterioles, forming concentric or lobular aggregates. Scattered through the larger masses of cells were small vascular channels, and some of these appeared to contain hyaline thrombi. An occasional juxtaglomerular arteriole was aneurysmally dilated. In addition, scattered small arteries and arterioles within the kidney exhibited endothelial hyperplasia (fig. 6) which was occasionally associated with thrombosis.

The epithelium of many convoluted tubules contained brown granular pigment which stained positively for iron. Eosinophilic hyaline droplets were noted in epithelium of convoluted tubules. Hyaline and cellular casts filled many collecting tubules.

Sections of bone marrow from vertebral bodies, iliac crest, sternum, rib, and femur all demonstrated marked hyperplasia. This appeared to be predominantly erythroid, but significant myeloid hyperplasia coexisted. Megakaryocytes appeared to be present in usual numbers.
Case 2 (W. B.) (SMH Unit No. 430918)

Forty days after the first symptom this 10-year-old white girl died of an illness characterized by hemolytic anemia, thrombocytopenia and renal failure.

Except for her third year of life the patient had always been in apparent good health. During that year she was hospitalized three times: once for malnutrition, once for tonsillectomy and adenoidectomy when she was said to have had "rheumatic chorea," and, finally, for bronchitis. At the time of these hospitalizations hemoglobin determinations were between 10.0 and 10.5 Gm. per cent, and all urinalyses were normal. Neither thrombocytopenia nor morphologic abnormalities of erythrocytes were noted.

After this difficult year she appeared healthy for seven years until February 1957 (age 10) when she developed occipital headache, epigastric pain, and vomiting. These symptoms persisted for seven days, and she was then admitted to her community hospital.* At that time the following laboratory data were obtained: hemoglobin 3.6 Gm. per cent, reticulocyte count 7.4 per cent, and platelet count 52,000. Urinalysis showed albuminuria and hematuria. She was transfused with 1500 ml. of blood during an 18-day hospital stay. On the 18th hospital day she had a grand mal convolution and was transferred to the University of Rochester Medical Center.

On admission to the hospital she appeared chronically ill. She showed signs of weight loss and was drowsy, but coherent. The blood pressure was 118/78. There was moderate pallor but no icterus. There was no external evidence of bleeding except for a few petechiae on the uvula and a few small retinal hemorrhages. The funduscopic examination showed some tortuosity of the vessels but no spasm. There was no papilledema. The liver was not palpable; the spleen tip was felt. The neurologic examination was normal.

The peripheral blood smear revealed marked thrombocytopenia; there was definite spherocytosis, and a moderate number of "irregularly contracted" erythrocytes were seen (fig. 1). Hemoglobin was 11.3 gm. per cent, hematocrit 30 per cent, and reticulocyte count 4.7 per cent. (These data were obtained one day after a transfusion.) The white blood cell count was 6,400, and the differential count and morphology of the white cells were normal. The urine sediment contained broad, coarse granular casts, tubular cell casts, and many erythrocytes. There was 4+ proteinuria. The stool did not contain blood. The blood chemical determinations indicated a high degree of renal insufficiency: NPN 126 mg. per cent, serum calcium 5.8 gm. per cent. The total bilirubin was 0.8 mg. per cent. Suspension of the patient's erythrocytes in a serum-albumin mixture, polyvinylpyrrolidine, and antiglobulin serum failed to reveal erythrocyte sensitization. No free serum antibodies were detected active against normal erythrocytes in preparing blood for transfusion (albumin and indirect antiglobulin cross-match). Presumptive tests for paroxysmal nocturnal hemoglobinuria and paroxysmal cold hemoglobinuria were negative. Two "L.E." preparations were negative. Heinz bodies were not seen. The osmotic fragility test revealed increased fragility of the patient's erythrocytes.

An aspirated bone marrow sample showed an increased number of normal-appearing megakaryocytes and erythroid hyperplasia.

Biopsy of an axillary lymph node showed reticular hyperplasia. Sections of biopsy material from skin, muscle, and bone marrow showed no sign of inflammation or thrombotic change in the small vessels.

The child's course was one of progressive deterioration. She was transfused after six days, during which time her hematocrit fell from an original value of 30 per cent to 15 per cent. Prior to the transfusion the reticulocyte count ranged from 4.7 per cent to 8.6 per cent. Progressing renal failure was reflected by increasing azotemia (NPN 228 mg. per cent) and hyperkalemia (potassium 9.2 mEq./L.). Although there was progressive azotemia, there was no change in the degree of thrombocytopenia or the degree or character of the morphologic abnormality of erythrocytes. In spite of appropriate fluid and electrolyte ther-
apy she became delirious, then comatose, and after convulsing intermittently for about one and a half days, died on the 15th hospital day. Neither fresh external signs of bleeding nor fever was noted during this entire hospitalization.

**Autopsy Findings (A-16893)**

At autopsy the body was that of a thin, slight, white female of 10 years. No petechiae or other signs of external bleeding were evident. The abdominal cavity contained 200 cc. of clear, straw colored, watery fluid. The walls of the gall bladder and intestine were edematous. The spleen was not enlarged.

The kidneys weighed 130 Gm. each. The surfaces of both kidneys were smooth, tan, and studded with pinpoint, bright red, slightly raised foci interpreted as congested glomeruli. Cortical striations were indistinct. Vascular lesions were not identified within the kidney at the time of autopsy.

All other viscera were unremarkable.

Microscopically, large amounts of brown, iron-containing pigment were found in reticuloendothelial cells of liver and spleen. Small amounts of fat were present in hepatic parenchymal cells. A section of vertebral bone marrow revealed a moderate increase in cellularity. The increase in cells was due principally to an increase in normoblastic erythroid precursors. Megakaryocytes appeared normal in number and morphology.
Striking alterations were present in both kidneys, with the most conspicuous changes found in the glomeruli and in small arteries and arterioles. Changes involved nearly all glomeruli, characterized principally by marked proliferation of cells of the glomerular tuft, with obliteration of many of the capillaries, fusion of the tufts, and cellular adhesions between tuft and capsule. Proliferation of capular epithelium was also noted. Some of the cells of the glomerular epithelium were markedly increased in size, and a few lay free in Bowman's space. The majority of hypercellular glomeruli appeared bloodless. Eosinophilic amorphous thrombi occluded capillary channels in some glomeruli, while other capillaries were severely congested. Hemorrhage into Bowman's spaces was present in a few instances. Scattered glomeruli exhibited mild patchy thickening of basement membranes. No significant leukocytic reaction was observed within glomeruli.

Extreme morphologic changes characterized the arterioles and small arteries of both kidneys. The principal alteration consisted of marked concentric cellular intimal proliferation, so severe as to all but obliterate many lumina (fig. 7). Vacuolated, lipid-containing cells were numerous in the proliferated intimal tissue, together with collections of extravasated erythrocytes (fig. 8). A few of the arterioles were occluded by thrombi, and most of these were located adjacent to glomeruli (fig. 5). Associated with the thrombi in juxtaglomerular sites, cellular proliferation of the type described in detail in relation to Case 1

Fig. 2.—Peripheral blood film from a patient who died of eclampsia (courtesy of Dr. Russel Weisman). A spherocyte and several "irregular contracted" erythrocytes are seen. X 256.
Fig. 3.—Case 1. The juxtaglomerular arteriole is aneurysmally dilated, filled with fibrin thrombus, and endothelial proliferation is present along one-half of arteriolar circumference. H & E X 64 (reduced).

Fig. 4.—Case 1. A spherical mass of endothelial cells is present at the vascular pole through which traverse several capillary channels. The glomerulus shows focal scarring. H & E X 64 (reduced).
Fig. 5.—Case 2.—A fibrin thrombus is present in juxtaglomerular arteriole, and there is slight endothelial proliferation occurring. H & E X 64 (reduced).

occurred, although to a much smaller degree. None of the vascular lesions was associated with the presence of an inflammatory cell infiltrate.

The tubular changes observed were noted principally in the proximal convoluted tubules where large amounts of iron-containing pigment were seen within the epithelium and within cells lying free in tubular lumina. Some tubular lining cells contained eosinophilic hyaline droplets. Hyaline and cellular casts were seen in large numbers in dilated convoluted and collecting tubules, together with small numbers of erythrocytes.

No significant histologic abnormalities were discovered in any of the rest of the organs examined, including striated muscle, lymph node and tonsil. No thrombotic, proliferative, degenerative, or inflammatory changes were evident in extrarenal vessels.

Review of Childhood TTP

We have found nineteen reports of thrombotic thrombocytopenic purpura (TTP) occurring in children under the age of 16 where the diagnosis was based on histopathology of blood vessels. (table 1 and Appendix.) All but one of these children died of the disease, and, of the deceased patients, the longest duration of recognized illness was four months. The single living patient7 was alive two years after the diagnosis had been established by the histologic appearance of lesions in pericapsular arterioles of a lymph node.

Except for the first year of life, cases of TTP in childhood appear to be distributed by age in a random fashion. Six of the 19 case reports we reviewed, however, described TTP in children less than one year old.

All of the children with TTP were anemic, and 13 reports include data suggesting that the anemia was hemolytic. In no case is there good evidence
Table 1.—Summary of Laboratory and Clinical Features of 19 Children with TTP

<table>
<thead>
<tr>
<th>Hematopoietic</th>
<th>Anemia</th>
<th>Poikilocytosis</th>
<th>Reticulocytosis</th>
<th>Thrombocytopenia</th>
<th>Purpura</th>
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<tr>
<td>Proportion</td>
<td>19/19</td>
<td>11/11*</td>
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<th>Proteinuria</th>
<th>Casts</th>
<th>Azotemia</th>
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<tr>
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<td>13/14</td>
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<td>9/10</td>
<td>7/8</td>
<td>6/19</td>
<td>12/17</td>
<td>11/15</td>
</tr>
</tbody>
</table>

*Spherocytsis the only abnormality described in 3 patients.
| *Purpura considered minimal in 3 of those 17 patients.

for an immune mechanism causing hemolytic disease. In all cases in which the peripheral blood smear was described, abnormalities of red blood cell morphology were noted. The abnormal cells were usually called poikilocytes, but in three cases the only abnormality mentioned was spherocytsis.

Thrombocytopenia was present in every case and was associated with purpura or petechiae in every case except two. The severity of purpura was variable, however. In three cases, only occasional petechiae were present or purpura was described as minimal. The other 14 children had more pronounced manifestations of purpura.

Evidence of renal disease was present in 15 of the 16 cases in which either a urinalysis or a blood nitrogen concentration was reported. Hematuria and proteinuria were the most frequent findings; casts were present in nine patients, and azotemia was noted in seven. Two patients were anuric, and one was described as dying with azotemia.

Evidence of central nervous system disturbance was present in 15 of 19 patients. The bizarre transitory neurologic manifestations which are regularly seen in adults with TTP were described in less than one-half of the childhood cases. The relative infrequency of these manifestations in children seems less significant, however, if the age of the patient is considered. The detection of subtle signs and symptoms of neurologic dysfunction is difficult in infants, and, indeed, none of the six subjects less than one year of age was described as showing bizarre preterminal manifestations of neurologic dysfunction. In eight cases the only neurologic manifestations were coma and convulsions in the last few days of life.

Fever was present in eleven of the fifteen patients where the child's temperature was reported.

Discussion

1. Clinical Features

While the short duration of illness in our second patient is consistent with the reported experience of others, our first patient's prolonged course is clearly unusual in children. We have no proof that the first manifestations of disease in Case 1, appearing at 21 months of age, represented the same disease process which was seen terminally. It seems most likely to us, however, in
Fig. 6.—Case 1. A small renal artery demonstrates slight endothelial proliferation together with subendothelial deposition of fibrin-like material. H & E X 160 (reduced).

Fig. 7.—Case 2. Severe endothelial proliferation has occurred entirely within a small renal artery. The lumen is almost entirely occluded. H & E X 160 (reduced).
view of the recurring nature of the same major manifestations of disease, that the patient’s entire illness represents a single disease entity.

While the duration of illness was dissimilar in our two patients, they shared many clinical and pathologic features. Both patients had hemolytic anemia. In Case 2 there was a rapid fall in hematocrit in spite of reticulocytosis, and in the absence of bleeding. In Case 1 it was proved, by measuring the survival of transfused cells, that an extracorpuscular factor was, at least in part, responsible for the shortened erythrocyte life span. In both cases an erythrocyte antibody was sought but could not be demonstrated.

Both patients showed a striking degree of poikilocytosis in the peripheral blood smear (fig. 1). In general the poikilocytes were small and dense. Some of these erythrocytes had one to four angular or spiny projections and were similar to “pyknocytes” as described by Tuffy, Brown and Zeulzer. Other cells had an irregular but smooth outline, identical in appearance to the “triangular cell” described by Dacie as a type of “irregularly contracted erythrocyte.” Dacie acknowledges the presence of this particular cell in TTP and considers it a special type of schistocyte. Spherocytosis was clearly present in both patients and became more prominent in Case 1 during the late stage of her disease. Abnormal erythrocytes were most prominent in Case 1 and were present when other signs of disease activity—hemolytic anemia, thrombocytopenia, and urinary abnormalities—were present, but were absent when there was no other evidence of disease activity. Allison has emphasized the distortion and fragmentation of erythrocytes seen in six infants who also had thrombocytopenia, hemolytic anemia, and renal disease. Two of these infants died and had renal vascular lesions thought to be diagnostic of TTP. The other four patients survived the acute illness and are alive and well four years later. Gasser has also described poikilocytosis associated with hemolytic anemia and renal disease in five children. All five children died and had “bilateral renal cortical necrosis.” In one case there were also lesions in the kidney characteristic of TTP. As noted in our review of TTP in children, other authors have described poikilocytosis associated with TTP. We propose that morphologic changes in erythrocytes are helpful in diagnosing both the acute and chronic or relapsing form of TTP.

Interpretation of the abnormal “Heinz body test” in Case 1 (see Special Hematologic Studies) is not clear. This test measures the production of Heinz bodies in red cells after incubation with acetyl phenylhydrazine (APH). Patients with primaquin sensitivity are deficient in erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) activity, and they can be detected by the “Heinz body test” because, after incubation with APH, more than 35 per cent of their red cells contains five or more Heinz bodies. While our patient had five or more Heinz bodies in 90 per cent of her red cells after incubation with APH, erythrocyte G-6-PD activity was actually elevated. Although she did not have G-6-PD deficiency, she may have had a different metabolic defect that made her red cells unusually sensitive to APH. Alternatively, her erythrocytes may have been intrinsically normal but were damaged in vivo and rendered unduly susceptible to the action of APH. In an effort to demonstrate a toxic substance in the serum of Case 1, normal red blood cells and G-6-PD deficient
red blood cells were incubated with the patient's serum (Special Hematologic Studies). The methods used, however, failed to reveal a difference between the patient's serum and the control serum.

Circumstances did not permit study of Heinz body formation while the patient was in remission. It would seem important to study this phenomenon in cases of TTP to determine whether this is a constant finding in these patients.

While thrombocytopenia was present in both patients, they never had more than a few scattered petechiae. This is in keeping with the experience of others (see table 1) who indicate that, although thrombocytopenia was always present, in one quarter of the children with TTP purpura was either absent or minimal.

A more prominent feature of the illness in our two patients was kidney disease. One patient (Case 2) died after an illness characterized by evidence of severe renal insufficiency; the other patient had recurring episodes of hematuria and proteinuria, laboratory evidence of decreased renal function as measured by excretion and clearance tests, and finally anuria and azotemia in the last few days of life. Lukes et al.13 have recently described 49 cases of TTP in adults, of which 47 showed renal abnormalities. Our experience and the experience of others (table 1) indicate that in children, too, abnormal urinary findings are regularly seen. We share the emphasis of Lukes et al. that renal abnormalities are an important feature of TTP, and would further emphasize that in children with TTP the visible vascular lesions may be confined to the kidney.

Lukes et al.13 include fever in a diagnostic quintad that also includes anemia, neurologic symptoms and signs, thrombocytopenic purpura, and renal abnormalities. Our second patient was never febrile, and the first patient had a single temperature elevation the day prior to death. Four children are described in the literature (table 1) who did not have fever. Thus it seems that in children the presence or absence of fever is of no help in diagnosis.

The final component of the clinical quintad is evidence of neurologic dysfunction. The neurologic manifestations of TTP in adults have frequently been described as episodic and bizarre in nature. Our of our patients (Case 1) had transient neurologic manifestations (paresthesias and tinnitus) during her final months of life, and the second had a convulsion two weeks before death. Both patients had convulsions terminally.

We have previously emphasized1 the apparent association between infections and exacerbation of disease activity in Case 1. This association continued to be apparent to the time of death. A review of the pediatric cases suggests that this association may be common in childhood TTP.

2. Pathologic Features

The cardinal histologic feature of thrombotic thrombocytopenic purpura is the presence of occlusive vascular lesions involving small arteries, arterioles, and capillaries and characterized by the presence of an acellular, amorphous, or granular eosinophilic thrombus whose origin is the subject of speculation and conjecture. The specific fluorescence of these thrombi which occurs with labeled antisera against human fibrin and the negative reactions obtained with
labeled antisera against human platelets strongly supports the contention that these thrombi are not composed of platelets, but that a major component is fibrin. The initial event in the development of these lesions is still not known, although most investigators believe that the process affects the vessel wall primarily and that the thrombi develop as secondary phenomena.

The vascular lesions which have been reported in this disease include "prethrombotic" hyaline changes, focally destructive lesions of the vessel wall; extensively destructive lesions associated with vascular occlusion; endothelial proliferation in the absence of occlusion; and aneurysm formation. The present cases illustrate several features worthy of comment.

Case 1 illustrates some of the more typical lesions of thrombotic thrombocytopenic purpura. Aneurysms are present in the renal vessels near the arteriolocapillary junction, and thrombi occur scattered throughout many organs in a pattern which is consistent with previous descriptions of this disorder. The unusual aspect of this case is the presence of remarkable proliferative lesions at the arteriolocapillary junction of the glomerulus. These lesions appear to represent the end result of a sequence: thrombosis associated with injury of vessel wall, aneurysm formation (fig. 3), endothelial proliferation, secondary thrombosis, and, finally, further endothelial proliferation and recanalization of thrombi with the final development of lesions composed of a mass of endothelial cells through which traverse small capillary channels, which may or may not contain thrombi. Many of these lesions are as large as the glomeruli to which they are adjacent. See figure 4.

Case 2 in this report is illustrative of an extra-ordinary degree of endothelial proliferation. The vascular lesions are limited to the kidneys, involve small arteries and arterioles, and are frequently associated with thrombi. In addition, within some proliferative endothelial lesions are seen numerous foamy macrophages filled with lipid. The fibrin thrombi, necrosis of vessel walls, and foamy lipophages associated with endothelial proliferation present in these kidneys are strikingly similar to the vascular lesions of the placenta in eclampsia as described by Zeek and Assali (figs. 8 and 9). This reaction within renal vasculature is unique in our experience.

Other morphologic similarities between TTP and eclampsia include the occurrence of disseminated fibrin thrombi and renal cortical necrosis in both disorders. In addition to these morphologic similarities, there are certain hematologic features common to TTP and eclampsia. Thrombocytopenia and hemolytic anemia are not uncommon in eclampsia. Pritchard, Ratnoff, and Weisman studied 22 patients with eclampsia and pre-eclampsia seen over an eight-month period; seven of their patients had thrombocytopenia, and 15 had evidence of hemolytic anemia. Poikilocytosis, a common feature of TTP, is also seen in eclampsia. Dr. Russel Weisman has kindly sent us a blood smear from a patient with fatal eclampsia which shows both "irregularly contracted" erythrocytes and spherocytes (fig. 2). Seifel reported two patients with hemolytic anemia and thrombocytopenia associated with eclampsia, and described the red blood cells as showing "marked anisopoikilocytosis with helmet cells, triangular cells, schistocytes, and occasional spherocytes." Counihan and
Doniach have observed two fatal cases of eclampsia associated with hemolytic anemia, and Dacie has described the hematologic findings in one of these patients, noting thrombocytopenia and "distorted, contracted, and triangular forms among the red blood cells in the peripheral blood smear." We would suggest that more intensive studies of red cell abnormalities in eclampsia and TTP may shed some light on the pathogenesis of both diseases.

**SUMMARY**

(1) Two cases of thrombotic thrombocytopenic purpura (TTP) occurring in childhood are described. Case 1 is unique in that the patient survived for 12 years.

(2) The clinical features of 19 reported cases of TTP in children are reviewed.

(3) The presence of morphologic abnormalities of red blood cells and the regular occurrence of kidney involvement in this disorder is emphasized. In one patient (Case 2), histologic changes of the disease were limited to the kidney.

(4) Certain hematologic and histologic features shared by TTP and eclampsia are described.

(5) Unusual histologic lesions of renal vessels are described.

**SUMMARIO IN INTERLINGUA**

1. Es describite duo casos de purpura thrombocytopenic thrombotic (PTT) occurrente in juveniles. Caso 1 es unic in tanto que le patiente superviveva 12 annos.

2. Es revistate le characteristicas clinic de 19 casos de PTT in juveniles reportate in le litteratura.

3. Es sublineate le presentia de anormalitates morphologic de erythrocytos e le occurrentia regular de un interessamento del renes in iste disordine. In un del patientes del presente reporto (Caso 2), le alterationes histologic asociate con le morbo esseva restringite al renes.

4. Es describite certe characteristicas hematologic e histologic que occurre tanto in PTT como etiam in eclampsia.

5. Es describite certe inusual lesiones histologic del vasos renal.

**APPENDIX**

*Case 1 (S. J.) (SMH #354837)*

The first manifestation of disease appeared at the age of 21 months when she was hospitalized because of anemia which was associated with normoblastemia and an "elevated" icterus index. After a blood transfusion she remained in apparent good health for four years when she was again hospitalized, at the age of six, with anemia. The anemia proved to be hemolytic in nature, due at least in part to a nonimmune extracorpuscular factor, and was characterized by the presence of small, dense erythrocytes possessing angular projections ("irregularly contracted" erythrocytes). Associated with the ane-
Fig. 8.—Case 2. Foamy lipophages fill much of the lumen of a small renal artery. Compare with figure 9. H & E X 205 (reduced).

Thrombocytopenia and urinary abnormalities characterized by proteinuria, microscopic hematuria, and hyaline and granular casts. During the ensuing one and one-half years there were several episodes of hemolytic anemia, thrombocytopenia, and evidence of renal disease; these episodes were separated by periods of good health when no abnormalities could be demonstrated in the blood or urine.

At age seven splenectomy was performed. At that time no vascular lesions were seen in specimens of skin, skeletal muscle, liver, kidney, and spleen.

Between the age of seven and one-half and 11½ years she was in apparent good health, and no urinary or hematologic abnormalities were noted on four occasions.

At age 11½ (November 1957), after four years of apparent good health, she was admitted to the Warsaw Community Hospital with complaints of fever, sore throat, and dark urine. Urinalysis showed 4+ proteinuria and microscopic hematuria; the blood nonprotein nitrogen was 96 mg. per cent. The platelet count was 26,000, and the hemoglobin concentration fell from 12.0 Gm. per cent on admission to 6.3 Gm. per cent on the fifth day. She was treated with penicillin and a blood transfusion and showed continued improvement so that after 16 days she was discharged when the urinalysis was normal and the hemoglobin concentration was 10.6 Gm. per cent.

She was seen one month after this hospitalization when the hematocrit was 31, the erythrocytes showed marked poikilocytosis with moderate spherocytosis, and the reticulocyte count was 7.4 per cent. The urine contained a trace of protein and an occasional hyaline cast but was otherwise normal.

Although no laboratory data are available, she felt well for about 18 months
when, at age 13 (May 1959), she developed a febrile illness without other signs of infection, and was admitted to the Warsaw Community Hospital. Urinary abnormalities (4+ protein, microscopic hematuria), moderate azotemia (NPN 69 mg. per cent), anemia, and thrombocytopenia were again noted, and the morphology of the erythrocytes was described as follows: "Marked anisocytosis, moderate poikilocytosis and polychromatophilia; four nucleated red blood cells. Many cells are in fragments." Again there was gradual improvement in the urinary and hematologic abnormalities over a period of five weeks so that at the time of discharge the urinalysis was normal and the hemoglobin was 15.2 Gm. per cent. The NPN, however, was 44 mg. per cent (normal 25–35 mg. per cent).

Three months later (August 1959) she was noted to be anemic (hemoglobin 10.5 Gm. per cent), morphologic abnormalities of erythrocytes were noted, and proteinuria and mild azotemia (NPN 43 mg. per cent) were present.

In November 1959, at age 13½, the patient was admitted to the University of Rochester Medical Center with a history of recurring severe headaches, occasional episodes of vomiting, increased fatigability, periodic paresthesias of the right hand, and intermittent tinnitus. The blood pressure was 140/90 and remained at this level. Her temperature was 37.4, and she remained afebrile. She appeared small and pale. There was no evidence of purpura, and no objective neurologic abnormalities were present. The hematocrit was 29 per cent, and hemoglobin concentration was 8.6 Gm. per cent. The white blood cell count was 14,200, and the distribution and morphology of the white blood cells was normal. The platelets on capillary blood smear were moderately decreased in number. Reticulocytes remained at a level of about 2 per cent. Many microspherocytes and "irregularly contracted" cells were seen on the
## Clinical and Laboratory Features of 19 Children with Thrombotic Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Duration</th>
<th>Preceding Infection</th>
<th>Anemia</th>
<th>Polyclonal</th>
<th>Reticulocytosis</th>
<th>Thrombocytopenia</th>
<th>Purpura</th>
<th>Hematuria</th>
<th>Proteinuria</th>
<th>casts</th>
<th>Anemia</th>
<th>Preterminal</th>
<th>Terminal</th>
<th>Fever</th>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>0</td>
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</tr>
<tr>
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<td>11 yrs.</td>
<td>F</td>
<td>3 wks.</td>
<td>URI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<tr>
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<td>1½ yrs.</td>
<td>F</td>
<td>2 wks.</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>8 yrs.</td>
<td>M</td>
<td>3 wks.</td>
<td>URI</td>
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<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>22</td>
<td>10 mos.</td>
<td>F</td>
<td>6 wks.</td>
<td>diarrhea</td>
<td>+</td>
<td>+ (S)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>-</td>
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<tr>
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<td>F</td>
<td>3 wks.</td>
<td>0</td>
<td>+</td>
<td>+ (S)</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
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<td>15 yrs.</td>
<td>F</td>
<td>4 wks.</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<tr>
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<td>M</td>
<td>16 wks.</td>
<td>URI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<td>M</td>
<td>Living</td>
<td>0</td>
<td>+</td>
<td>+ (S)</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>22 mos.</td>
<td>F</td>
<td>1 wk.</td>
<td>diarrhea</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>11 yrs.</td>
<td>M</td>
<td>4 wks.</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>-</td>
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<tr>
<td>26</td>
<td>10 mos.</td>
<td>F</td>
<td>4 wks.</td>
<td>diarrhea</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>27</td>
<td>11 yrs.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<tr>
<td>28</td>
<td>7 yrs.</td>
<td>F</td>
<td>2 wks.</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>29</td>
<td>15 yrs.</td>
<td>F</td>
<td>12 wks.</td>
<td>URI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>10</td>
<td>2 mos.</td>
<td>F</td>
<td>1 wk.</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>-</td>
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</tr>
<tr>
<td>10</td>
<td>6 mos.</td>
<td>M</td>
<td>1 wk.</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>4 wks.</td>
<td>0</td>
<td>+</td>
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<td>+</td>
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<td>0</td>
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<td>0</td>
<td>-</td>
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<td>+</td>
</tr>
<tr>
<td>Case 1</td>
<td>13 yrs.</td>
<td>F</td>
<td>12 yrs.</td>
<td>URI</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Case 2</td>
<td>10 yrs.</td>
<td>F</td>
<td>6 wks.</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = present.  
- = absent.  
0 = not described.  
++ = present, but minimal.  
(S) = spherocytosis only abnormality mentioned.
peripheral blood smear, and this finding persisted to the time of her death. The direct antiglobulin test was negative. Urinalysis revealed 2 to 3+ proteinuria, microscopic hematuria, and 5 to 15 white blood cells and an occasional granular cast per high power field. Studies of kidney function revealed (1) normal intravenous pyelogram, (2) excretion of 35 per cent PSP in one hour, (3) urea clearance test of 40 per cent of normal, and (4) creatinine clearance of 50 per cent of normal. Blood nonprotein nitrogen concentration was 32 and 50 mg. per cent on different days.

The total serum bilirubin concentration was 1.0 mg. per cent of which 0.7 mg. per cent was indirect. Serum transaminase (SGOT and SGPT), alkaline phosphatase, and thymol turbidity determination were all normal. Cephalin flocculation was 2+. Serum protein electrophoretic determination and urinary catechol amine concentration were normal.

Her presenting symptoms abated during this hospitalization, and she was discharged on no medication. At home she remained lethargic, sleeping as much as 16 hours a day. When seen one month after the last hospitalization she appeared chronically ill, and her blood pressure was 150/110. Anemia, poikilocytosis, leukocytosis, reticulocytosis, thrombocytopenia, and proteinuria were noted.

Another month later (February 1960), two weeks after a "flu-like" illness, the patient was admitted for a final hospitalization. In addition to previous complaints of lethargy and headache she now complained of blurring of vision in the right eye. The blood pressure was 140/110 and the temperature 37.5 C. She appeared chronically ill and was drowsy but coherent. Two petechiae were seen. The remainder of the physical examination was not remarkable. The hematocrit was 20 per cent, and hemoglobin concentration was 7.1 gm. per cent. The WBC was 27,000 with a mild "left shift," and after five days the WBC was 59,000 with a pronounced "left shift." Marked thrombocytopenia and the abnormal erythrocyte morphology previously described were present. Urinalysis showed 4+ proteinuria, microscopic hematuria, and one to two granular casts per high power field. The blood nonprotein nitrogen content on admission was 42 mg. per cent. Serum chemical determinations revealed normal liver function and normal electrolyte concentrations.

She remained lethargic, and on the fifth hospital day labored respirations began, followed by coma and then convulsions. Anuria, associated with a rise of blood NPN to 82 mg. per cent, was noted. A lumbar puncture yielded clear fluid under normal pressure. There were no cells in the cerebrospinal fluid, and values for glucose, protein, and chloride content in the cerebrospinal fluid were normal. The patient continued to decline, and she died on the sixth hospital day. There was a single temperature elevation to 40.3 C. on the day prior to death, but she was otherwise afebrile. There was no sign of purpura during this final hospitalization except for two petechiae.

ADDENDUM

Theil et al.\(^3^\) have reported altered stability of reduced glutathione (GSH) in patients with acute and chronic renal insufficiency. In our patient (Case 1) the GSH stability test was normal during the chronic phase of her disease: erythrocyte GSH content before incu-
bation with acetylphenylhydrazine (APH), 68 mg. GSH/100 ml. RBC (normal = 74 ± 9 mg. GSH/100 ml. RBC), and after incubation with APH, 66 mg. GSH/100 ml. RBC (normal = 66 ± 9 mg. GSH/100 ml. RBC).

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REFERENCES

11. —: Personal communication.
TTP IN CHILDHOOD


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Thrombotic Thrombocytopenic Purpura in Childhood

JAMES B. MACWHINNEY, JR., JAMES T. PACKER, GERALD MILLER and ROBERT M. GREENDYKE

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