The Diffuse Vascular Lesion of So-Called “Thrombotic Thrombocytopenic Purpura”

By Harold W. March, M.D.

“Thrombotic thrombocytopenic purpura” is a thrombocytopenic, hemolytic disease with occlusive mounds in the arterioles and capillaries. These mounds have been popularly supposed to represent bland platelet thrombi. In recent years observations have been forthcoming in favor of a primary bland lesion as the anatomic basis of the disease. This paper places special emphasis on the latter proposition, and pathologic material is presented to demonstrate how such a lesion probably evolves.

RECENT studies by pathologists, together with data from collateral sources, have made it apparent that the clinical disease now familiar to clinicians as “thrombotic thrombocytopenic purpura” is the result of primary damage to blood vessels, and should be included in the group of “diffuse vascular diseases.”

First reported in the medical literature 27 years ago, its true character and morbid anatomy went long unappreciated by clinicians who confused it with idiopathic thrombocytopenic purpura, and by pathologists who interpreted the verrucal masses in dilated arterioles and capillaries as bland platelet thrombi. These misconceptions are currently in the process of being rectified. As a result antemortem diagnosis is feasible at the present time, and the primary degenerative change in the terminal blood vessels will soon be more generally appreciated.

HISTORICAL BACKGROUND

The obstacles to understanding this lesion were actually quite formidable. It was presented to medicine at a time when the concept of connective tissue ground substance as the site of biochemical and histologic abnormalities had not been widely adopted. Gerlach was still developing his ideas on connective tissue injury in the Arthus phenomenon, and Klinge had not published his monograph on rheumatic fever and the rheumatic diseases. In this country, though Libman and Sacks had recently described the heart in disseminated lupus erythematosus, it was not until 1941 that the pathology of lupus was understood as a morbid process localized in the connective tissues.

The original description of the disease is credited to Moschowitz in 1925.19 His patient was a 16 year old girl with a two week course of weakness, pallor, fever, petechiae and profound anemia. No platelet count was recorded, but the hemoglobin was 40 per cent and the red blood cell count was 1,330,000 per cu.mm. The gross autopsy findings were not distinctive, but on microscopic examination Moschowitz saw what he interpreted as thrombi in the terminal arterioles and capillaries. The “thrombi” were surrounded by cells which he identified as fibroblasts. Fibroblastic penetration of the mass was noted with eventual formation of tuberculosis like structures. Later observers have demurred from this interpretation of the cells seen capping the “thrombus.” Impressed by the work of Flexner with red blood cell toxins, Moschowitz concluded that the “thrombi” consisted of agglutinated and hyalinized erythrocyte masses and called the disease “an acute febrile pleiochromic anemia with hyaline thrombosis,” caused by a powerful toxin with both agglutinative and hemolytic properties.

A different mechanism was proposed in

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1936 by Baehr, Klemperer and Schiffrin. They reported four cases in young and middle aged females with fulminant purpura hemorrhagica, thrombopenia, progressive anemia and prominent cerebral symptoms. They found innumerable hemorrhages in all serous and mucous membranes and within many viscera. Microscopically they observed thrombotic and proliferative lesions, most commonly in the arterioles and capillaries of the kidneys, heart, adrenals and pancreas. Proliferative changes in the lining endothelium of the involved vessels were seen, with actual invasion of the thrombotic mass, but they did not find evidence of organization. It was noted that in some areas the endothelial activity was out of proportion to the amount of thrombosis whereas in other situations the reverse was true. No parenchymatous changes were observed. The “thrombi” did not stain for iron or hemoglobin, and from the Giemsa stain it was concluded that they consisted of platelets. The thrombopenia was regarded as secondary to withdrawal of platelets into the occluding masses. Since the Giemsa stain cannot be considered specific for platelets the conclusions of these workers rested on very tenuous grounds.

In the same year Friedberg and Gross published a series of papers on nonbacterial thrombotic endocarditis associated with acute thrombocytopenic purpura, and with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions. One case in the former report was actually included in Baehr’s protocols. The latter paper included at least one example of the disease under discussion. Case 2 of that group suffered from fever, profound anemia, and transient cerebral palsy, a combination later to be remarked upon many times in the clinical characterization of the disease. The “hyaline and granular plugs” in the heart, lungs, pancreas, thyroid and spleen leave little doubt about the identity of the lesions. Interestingly enough, Gross and Friedberg did not believe that the plugs were thrombotic. In ascribing them, on at least one occasion, to proliferation and desquamation of endothelium, they propounded the first definitely vasculogenic view of the lesion.

The next communication pertaining to this entity was that of Gitlow and Goldmark in 1939. Their effort was vitiated by the failure to clearly distinguish this disease from disseminated lupus erythematosus. Indeed, their second case was disseminated lupus with severe “wire loop” lesions in the glomeruli simulating thrombi.

During the following decade observations were made by a number of investigators, and by 1950 24 cases of the syndrome were available for analysis. Almost without exception endothelial proliferation was noted in and about the lesions and discussion concerned itself mainly with the significance of this finding. Thus Altschule gingerly implied the presence of endothelial damage but pointed out that the origin of this damage was unknown. Conversely, Green and Rosenthal and Bernheim were unable to find endothelial aberrations where no “thrombi” were present, and the latter concluded that there was no morphologic evidence for endothelial disease. Trobaugh’s conclusions were essentially similar in that he regarded the process as being thrombotic. Fitzgerald in reporting three cases observed occasional independent endothelial changes but on the whole there were “overwhelmingly more thrombi,” and referred to the disease as “thrombocytic aeroangiothrombosis.” Employing differential stains for erythrocytes, hemoglobin, leukocytes, fibrin, bacteria and inclusion bodies, he decided, as Baehr and coworkers had done, that the masses were composed of platelets. Singer’s conclusions were quite similar, and he contributed the popularly employed designation for the disease, “thrombotic thrombocytopenic purpura.”

However, observations critical of these formulations were not long in appearing. Muirhead was impressed with the prominence of endothelial proliferation in his material, and Engel noted swelling and proliferation of the capillary membrane. More significantly in Engel’s slides, the blood vessel wall adjacent to the plugs showed degenerative changes and a few were frankly necrotic. This was especially prominent in the heart, kidneys and adrenals, though almost every
organ was involved. At approximately the same time Carter\textsuperscript{59} found conspicuous fibrinoid degeneration in the arterioles of the heart and kidneys, without any evidence of surrounding inflammation. Plugged vessels were most numerous in the heart, kidneys, adrenals, spleen and brain. There was, however, no modification of the “thrombotic” theory.

Evolution of Present Ideas

The work of Gore\textsuperscript{32} represented a step away from the simple “thrombotic” formulation. In studying five cases at the Army Institute of Pathology he found focal, “prethrombotic” lesions of the vessel wall. In essence it was described as a segmental accumulation of hyaline beneath the endothelium of a capillary and between the endothelium and media of an arteriole, usually the latter. The homogeneous substance tended to swell luminally, carrying before it an unaltered endothelium, and adventitiously, producing a defect in the vessel wall. This swelling was thought to be due to imbition of fluid from the circulation. When the process occurred rapidly the endothelium was broken, platelets accumulated over the defect, and the inaccessibility of antithrombic substances assured propagation of a thrombus which received a prompt endothelial investment. Lesions appeared to be in different stages, some showing organization and fibrosis, suggesting that the process had occurred in showers. Gore then clearly stated for the first time that the initiating factor was a focal vascular lesion.

At the same time Gore had accepted the conventional view that the verrucal portion of the lesion consisted of platelets. This point was examined critically in two papers by Meacham\textsuperscript{57} and Orbison.\textsuperscript{55} They stated unequivocally that “thrombotic thromboeytopenic purpura” is a collagen disease in which blood vessel damage is the primary event. They found characteristically an eosinophilic, smudgy (fibrinoid) mass replacing the normal fibrillar and cellular structure of the wall of involved arterioles and capillaries. The process was focal and segmental, and was seen occasionally without the intraluminal mound. When occlusions were present, these had the same tinctorial characteristics as the intramural fibrinoid material and appeared to be continuous with it. By camera lucida reproductions of serial sections Orbison\textsuperscript{55} demonstrated a remarkable feature of the lesion in all organs, namely dilatation and cylindric aneurysm formation at the arteriolo-capillary junction. Where the verruca joined the vessel wall, the elastica was destroyed and the media showed eosinophilic homogenization. It was concluded that such destruction and dilatation could not be caused by thrombi alone, and that the mural lesion was fundamental. However, an additive role by platelets in the formation of occlusive mounds could not be excluded. In discussing the difficulties pertaining to this matter, the above workers reiterate that platelets cannot be made to stain specifically. In their hands, the hematoxylin and eosin and periodic acid Schiff stains colored the mural and intraluminal material identically. Moreover when material from the lesions was compared with a suspension of platelets, and with the lesion of periarteritis nodosa tinctorially, they could not be distinguished, either by the periodic acid Schiff or Feulgen technics. Platelets, verrucal angioneerosis and amyloid stained metachromatically with toluidine blue, but there was no metachromasia with periarteritis material. Thus the reactions are parallel but not specific. Interestingly enough, though most studies of the subject continue to refer to “thrombotic thromboeytopenic purpura,”\textsuperscript{57, 10, 14, 21, 27, 31, 39, 58, 66, 67, 70, 71, 74, 75, 76} a few of these include photomicrographs showing very clearly degenerative changes in the vessel wall underneath the “thrombus.”\textsuperscript{51, 30, 71}

In 1951, Allen referred to the disease under discussion as “arteriole-capillary thrombonecrosis.” It was regarded as a “diffuse vascular disease,” with fibrinoid degeneration of mural collagen and dilatation of terminal vessels as the primary event. Recently he has employed the term “thromboeytopenic verrucal angioneerosis”\textsuperscript{58} which he considers a more appropriate name. Allen considers that the verrucal lesion is almost exclusively a propagation of degenerated, swollen collagen, with only a negligible contribution of plasma, fibrin and
formed elements from the blood. This author likens the problem to that of degenerative verrucal endocardiosis (nonbacterial thrombotic endocarditis, terminal or marantic endocarditis), also long regarded as a thrombotic valvular accretion of elements from the circulation. Systematic investigation with stains for collagen before and after tryptic digestion indicated very clearly that the verruca originated from degenerated valvular collagen and were aggranized in only minor degree by plasma and cellular elements from the injured capillaries of the valve.

The relevance of these investigations to "thrombocytopenic verrucal angioneurosis" is further underscored by the appearance in the latter disorder of atypical endocarditis. In one instance it appeared to be superimposed on a healed rheumatic valvulitis, and in still another it was associated with Staphylococcus aureus endocarditis. Where detailed description of these vegetations is available, it is apparent that the verruca being described are the same as those appearing in degenerative endocardiosis. They are irregular, often large and friable, and have little or no tendency to extend on to the mural endocardium. Histologically they are a bland degeneration of collagen, lacking the granulomatous and vascular granulation elements of rheumatic fever, or the inflammatory-degenerative character of the Libman-Sacks endocarditis with its prominent cellular necrosis and hematoxylin body formation. And just as degenerative verrucal endocardiosis occurs in a variety of chronic infectious, degenerative, or neoplastic conditions, especially if rheumatic infection has deformed the valve, so verrucal angioneurosis may appear under very similar circumstances. Although limited mainly to the heart, in these circumstances, it is morphologically indistinguishable from lesions seen in clinically fulminating thrombopenia and anemia. Furthermore it has been described in the pathology of typhus fever. Baehr and his colleagues have also pointed out that inflammatory or thrombotic changes in a few vessels are frequently encountered in almost any type of infection, and Page described similar plugs in the terminal vessels in subacute bacterial endocarditis. Indeed it would be of interest to study the incidence of thrombopenia and bleeding tendencies in a large group of patients who have long-term illnesses not directly involving the blood-forming organs, to determine whether these can be correlated with the appearance of verrucal lesions. Actually such a mechanism is not required to explain the thrombocytopenia here any more than it is necessary in idiopathic thrombocytopenic purpura where no lesions are found, or in disseminated lupus where one also frequently encounters thrombopenia and even sporadic verrucal angioneurosis. For the recent work done on gamma globulin factors in lupus erythematosus, idiopathic thrombocytopenic purpura, and acquired hemolytic anemia, indicate that abnormal immune globulins are responsible for diverse tissue and marrow alterations. Similar mechanisms may be operating in fulminating "thrombocytopenic verrucal angioneurosis" and in certain patients with chronic illnesses who develop endocardiosis and angioneurosis.

The relationship of this disease to disseminated lupus erythematosus has been suggested. It is true that superficial similarities exist. Both occur in young women, and lupus may be associated with thrombopenia, hemolytic anemia or occluding vascular lesions, while verrucal angioneurosis may exhibit endocarditis, or, rarely, periarteriolar splenic fibrosis. At first blush this seems to make an impressive case, but the evidence does not remain convincing. The predominance of females over males is no longer as great in either disease as originally reported. The thrombopenia and hemolytic anemia are manifestations of disordered immune processes and cannot be given a more specific interpretation. The bland endocarditis in verrucal angioneurosis is quite different from the florid, alterative lesion of Libman-Sacks endocarditis, and in disseminated lupus the verrucal angioneurosis is inconstant, limited to the heart, and usually seen only when endocarditis is also present. Finally periarteriolar fibrosis in the spleen has also been reported in three cases, but in one case the angioneurosis...
was limited to the heart and stigmata of lupus erythematosus were present, and in a second case it was only suggestive. Finally, though periarteriolar fibrosis is seen characteristically in lupus, it has been reported in other conditions and its specificity has been questioned. Most writers now deny that the two diseases are related.

CLINICAL FEATURES

The diagnosis of “thrombocytopenic verrucal angioneurosis” is a challenge to the acumen of the clinician. Malaise, weakness, arthralgias, generalized body aches, headache and dizziness are fleeting prodromata. Antecedent upper respiratory infection is significantly frequent. Of the first 15 cases reported, 11 were females and four were males, but more recently the sex predilection has not been so striking. Seventy-five per cent of the first 15 cases were less than 35 years of age, but in later reports the proportion of patients between 40 and 60 years has risen. No race predilection has been established.

The prodromata soon give way to a hemorrhagic disease of explosive character, terminating in death within a few weeks of the onset. Ecchymoses and purpura appear on the skin, and epistaxis, hematuria and melena indicate diffuse bleeding from mucous membranes. These are usually present when the patient is first seen by the physician. In addition, pallor is striking and may even antedate the bleeding, further evidence of a hemolytic process. Mild acholuric jaundice may accompany the pallor. The temperature is variable, low grade fever being present early in the disease, but a temperature of 106–107°F. terminally may be found, and indicates hemorrhage into the brain. The liver and spleen are palpable in about 50 per cent of the cases. Neurologic findings are of constant occurrence and figure predominantly throughout the course of the illness. The most common of these are headache, confusion, delirium, stupor, reflex changes, hyperesthesia, convulsions, facial weakness, hemiplegia, and coma. Occasionally neuropsychiatric symptoms initiate the illness. One patient was admitted in stupor and two in semicoma. In another case paranoid ideas were the presenting symptom, and still another patient was admitted to a mental institution for depression. An often mentioned characteristic of the mental and neurologic features is their remittent nature; the most alarming symptoms may regress in a matter of days, to be replaced by still others. This is in contrast to idiopathic thrombocytopenic purpura, where neurologic changes are less frequent, and when present, non-remitting. Excellent reviews of the neurologic aspects have been written.

Although in the majority of instances thrombocytopenic verrucal angioneurosis appears to arise de novo and run a fulminating course, occasional exceptions are noted. Meacham’s case lived for two years following splenectomy. In other instances patients were ill for a number of years with cardiovascular, renal, arthritic or allergic diseases (urticaria, sulfa sensitivity), and the distinguishing features of verrucal angioneurosis occurred only terminally, or at autopsy. In two patients the verrucal lesions were limited to the heart and skin, respectively. A case has been seen by the present author in which the lesions were limited to the kidney and heart. Amyloidosis of the secondary type was present. The patient was a 31 year old male patient who had been ill for seven years before death with intermittent migratory arthralgia, mitral murmurs and a fever of unknown origin. He had multiple admissions and finally died in heart failure with enlarged heart, pericardial friction rub, arthralgias, hemolytic anemia, purpura, and epistaxis. No platelet count was done. These experiences suggest that the lesion may occur in marked form as a terminal phenomenon and as a sequel to an antecedent disease, especially one of the collagen group. The patient cited above was thought to have rheumatic fever and rheumatoid arthritis.

LABORATORY PROFILE

The most constant laboratory findings are thrombocytopenia and hemolytic anemia. The anemia is usually normochromic with the hemoglobin dropping to 3 to 5 Gm. per 100 cc.,
and the red blood cells to 2.5 million per cu.mm. or lower. There is commonly a leukocytosis of 12 to 15,000 per cu.mm., and the differential count is shifted to the left. Nucleated red blood cells, reticulocytosis, inconstant spherocytosis and terminal leukemoid reactions are not uncommon. The platelet count may be only moderately depressed early in the disease, but counts of 30,000 per cu.mm. or less are the rule when the syndrome is well developed.

The hypotonic saline fragility is usually normal, but may be increased when spherocytosis appears. Singer found the acid (heat) fragility normal, but the mechanical fragility was definitely increased, suggesting the pattern of acquired hemolytic anemia to that investigator. The Coombs test was negative in his patient and others have had the same experience. The bleeding time is regularly increased and the tourniquet test is positive.

The bone marrow is usually hyperplastic and the megakaryocytes are normal or increased. Although Singer found normal platelet maturation, deficient or absent thromboocyte production was noted by Meacham, Barondess, Cooper, and Green, a situation similar to that found in idiopathic thrombocytopenic purpura. Cooper has found the pathogenic mononucleic vessel lesion in the marrow by examining paraffin sections of sternal aspiration material.

The serum bilirubin is usually elevated to 2.5 to 4.0 mg. per 100 cc. with the indirect reaction predominating. Fecal and urinary urobilinogen are increased, but Singer considers the acholuric jaundice to be a more constant indication of hemolysis. The total proteins and serum globulin may be elevated, but this is not a consistent finding. The “I.E.” cell test has been reported negative, but biologic false positives for syphilis are seen. The antemortem diagnosis of thrombocytopenic verrucal angioneurosis was first made by Engel in 1947, then by Singer in 1950. Meacham made it from splenectomy material in 1951. The disease simulates many of the hemorrhagic disorders and the diagnosis can be established only by close attention to clinical detail. The combination of acquired hemolytic anemia and thrombocytopenic purpura not readily explained by a history of toxins, drug idiosyncrasy or bone marrow invasion (tumors, lymphoma, leukemia, lipid histiocytosis, granulomata) should awaken suspicion. Idiopathic thrombocytopenic purpura is not usually associated with hemolytic anemia and the spleen is invariably not palpable. Fluctuating, transient neurologic signs are very characteristic of verrucal angioneurosis, and not at all frequent in idiopathic purpura in which central nervous system involvement, when it occurs, is usually in the form of severe hemorrhage. Finally the identification of the involved vessels in paraffin sections of marrow aspirates, as reported by Cooper, offers a promising approach. Meacham has suggested that the lesions might be found in skin biopsies.

### Prognosis and Treatment

This disease is uniformly fatal. One patient of Meacham's survived 2.5 years following splenectomy, but in every other instance the results of this procedure have been discouraging. Likewise corticotropin (ACTH) and cortisone have had no truly beneficial effects.

### Histogenesis

The histogenesis of verrucal angioneurosis is well demonstrated in the following case report.

The patient was a 29 year old male Italian leather worker admitted with a characteristic history of headache, bleeding gums, and sore throat for three days, and hematuria of 24 to 48 hours duration. He had pallor, purpura of the lower extremities and spongy, friable gums. The liver and spleen were not palpable.

Admitting laboratory data were as follows: Red blood cells 2.5 million per cu.mm., hemoglobin 8.0 Gm. per 100 cc., platelets 225,000 per cu.mm., white blood cells 12,000 per cu.mm., hematocrit 23 per cent. Examination of the urine showed 2 plus albumin, many white blood cells and red blood cells and occasional granular casts. The blood chemical findings were: urea nitrogen 21.6 mg. per 100 cc., total protein 7.2 Gm. per 100 cc., albumin 4.5 Gm. per 100 cc., globulin 2.7 Gm. per 100 cc., cholesterol 116 mg. per 100 cc., esters 78 mg. per
100 cc., cephalin flocculation test negative and alkaline phosphatase 3.4 mg. per 100 cc.

The patient ran a febrile course, 105°F., and rapidly deteriorated. There was continued hematuria and hemorrhage into the skin. The hemoglobin dropped to 3.6 Gm. per 100 cc., and the red blood cells to 1,300,000 per cu.mm. Icterus was present and the urine was positive for hemoglobin. On the tenth hospital day he developed right facial weakness and paralysis of the right arm. He died on the fourteenth hospital day in coma. The final hemoglobin was 3.6 Gm. per 100 cc., the platelet count was 14,650 per cu.mm., and the icterus index was 45.

At autopsy there were subconjunctival ecchymoses and purpura of the extremities. Hepatosplenomegaly was present. Petechiae and purpuric spots were found throughout the viscera, especially the heart and kidney. There was leptomeningeal hemorrhage over the left frontal pole and in the central white matter of the left frontal lobe. Smaller hemorrhages were found in the right hippocampal gyrus, in the marginal cortex of the right central and calcarine fissures, and on the left lateral aspect of the corpus callosum. They varied from a few millimeters to one centimeter in size. A few millimeter-sized hemorrhages were also seen in the right cerebellar peduncle.

Figure 1 is a photomicrograph of the kidney, showing a distal interlobular vessel in two sections. The section of vessel further from the glomerulus shows focal eosinophilic necrosis in its wall. This represents the earliest change. Note that at this point the wall of the vessel is slightly thickened. The intima is destroyed and the amorphous eosinophilic material bulges slightly into the lumen. Likewise the outer border of the vessel at the point of change is ragged and indefinite. The adventitia...
is not identified as a smooth line, and the eosinophilic material appears to merge imperceptibly with the perivascular tissue. The section nearer the glomerulus shows the lesion in a much advanced stage. The necrotic material has extruded itself into the lumen, forming a verruca mass capped with hyperplastic endothelial cells which have plump vesicular nuclei. There is no inflammatory reaction or scarring. Figure 2 shows the verruca lesion in capillaries of the heart. The intramural degeneration has greatly thickened the wall and bulged into the lumen, converting it into an eccentric slit. Note the continuity between the intraluminal material and the altered vessel wall. The capillary is also greatly dilated. Aneurysmal dilatation is an integral part of the process in consequence of connective tissue and elastic destruction. Figure 3 is an elastic stain of myocardium, showing the fraying and destruction of the elastica in the vicinity of the lesion. In figure 4 the neurogenic origin of the degenerated luminal mound is again demonstrated. Although the verruca originates at the site of vessel injury, it soon propagates down the lumen. This growth is due to further intramural connective tissue degeneration, to transudation of fluid from the blood, and probably to some accretion of fibrin and formed elements. This propagated portion of the "thrombus" is also rapidly endothelialized, forming a sleeve. Fortuitous sections through this portion show what appears to be a bland thrombus with no attachment to the vessel wall. Figure 5 shows such a bland "thrombus," in a dilated capillary, and with an endothelial investment. Although almost every vessel was involved in this case, there is no necrosis, fibrosis or infiltration of the myocardium or other organs (fig. 6).
Etiology and Pathogenesis

The etiology and pathogenesis of “thrombocytopenic verrucal angionecrosis” presents the same elusive complexities as those pertaining to the collagen diseases in general. In these disorders hypersensitivity may be suggestive or explicit, but the nature of the antigen has often evaded scrutiny, and the mechanism by which an antigen causes observable histopathologic changes remains obscure. In periarteritis due to sulfa,8 penicillin,7 horse serum,29 or iodine,60 for example, the nature of the antigen is apparent, as it also is with rheumatic fever which can be reproduced experimentally with heterologous streptococci20,24; so too with glomerulonephritis, which is producible with streptococci and serum49 or bovine globulin.73 In disseminated lupus erythematosus, on the other hand, the allergen is not apparent, but other considerations such as the antigenic nature of the L.E. cell80 make it permissible to classify it as a hypersensitivity disease, at least tentatively. “Thrombocytopenic verrucal angionecrosis” appears to occupy an intermediate position in this respect. Interestingly enough, siblings of patients with the disease have had idiopathic thrombocytopenic purpura,6 or died of disseminated lupus,85 or periarteritis nodosa.9

Two verrucal angionecrosis patients are known to have had antecedent rheumatic fever.7 23

Since this disorder is not a “thrombosis,” hypotheses relating to abnormalities of the blood clotting mechanism,9 13 or to endothelial toxins10 are not applicable. The Schwartzmann phenomenon29,61 as a possible prototype of the lesion has been adequately controverted by Gore.82

The almost constant occurrence of upper respiratory infection and pharyngitis shortly before the acute stage of the disease is striking,6,16,20,23,30,62,69. This is significant not from the point of view of viral or bacterial etiology, but because of possible hypersensitivity factors that infection might initiate. For patients with this disease often exhibit allergies and drug idiosyncrasies, and at times these might even be regarded as causative. Urticaria6,21 and adhesive tape dermatitis9 have been noted and in three patients small pox vaccine,33 tetanus antitoxin, and milk protein67 were administered shortly before the onset of the illness, and cannot be excluded as contributory factors. More constant and convincing is the sensitivity exhibited to sulfa,8,11,20,23,62,70 penicillin,27,70 and iodine.19 Usually the sulfa or penicillin were taken for an infection (respiratory, pharyngitis, arthritis, adenitis or genitourinary infection). The evidence of drug reaction such as chills, fever, malaise, arthralgias, diffuse skeletal pain and hematuria often directly antecedent the onset of the fatal disease. Ehrlich’s patient took a reducing drug containing 0.3 mg. of elemental iodine in each tablet.19

At autopsy the iodine was recovered from the tissues by chemical assay. Muirhead81 and Gore83 have reported glomerulonephritis in their cases, and this finding along with the thrombopenia and hemolytic anemia which are invariable features of the disorder may be interpreted as a manifestation of hypersensitivity. For though Bernheim8 could not demonstrate an antiplatelet factor in the postmortem blood of one patient and though the Coombs test was negative in the few instances when it has been done,7 27,47,62 too little attention has been given to the immunologic aspects of verrucal angionecrosis. Now that the diagnosis can be made ante mortem, opportunities will present themselves for further study, and it is likely that “factors” will be found just as they have been in idiopathic thrombocytopenic purpura22,36,65 and acquired hemolytic anemia.15

Finally though allergic evidence is impressive it is well to be circumspect in excluding other possible agents. For just as fibrinoid degeneration can be induced in blood vessels by nonantigenic methods,52 56 and periarteritis nodosa has been noted in rats in the presence of rapidly rising blood pressure,17 64 so the lesion of verrucal angionecrosis is seen in photomicrographs of vessels from dogs made hypertensive and azotemic by bilateral nephrectomy13,52,56 or other procedures resulting in hypertension.12 It is apparent then, that intravascular stress, azotemia, hormones,
pressor substances or other factors may produce the lesion of verrucal angioneurotic anemia, as well as those of periarteritis and malignant arteriosclerosis, and any truly valid pathogenetic concept must integrate all of these variables.

Summary

1. The purpose of this paper has been to support the thesis that so-called "thrombotic thrombocytopenic purpura" results from primary damage to arterioles and capillaries, and is therefore a "diffuse vascular disease."

2. The evolution of the literature on the subject has been traced, and a review of the clinical, laboratory and therapeutic aspects of the disease has been offered. As regards the historical development of the subject, special emphasis has been placed on the observations of Orbison, Meacham, and Allen, which suggest that primary damage to the terminal portions of the vascular system in many organs is the essential pathologic process.

3. A case which has come under the author's observation is presented in detail. From this material representative sections are employed to illustrate the histogenesis of the lesion from the early stage of intramural vascular necrosis to the fully developed and propagated "bland thrombus."

4. Although no abnormal globulin "factor" has been isolated in this disease certain clinical and hematologic characteristics suggest that it is related to diseases like acquired hemolytic anemia, thrombocytopenic purpura, and disseminated lupus erythematosus, in which abnormal immunologic mechanisms have been demonstrated.

Acknowledgment

The author wishes to express his gratitude to Dr. J. L. Orbison for reviewing the manuscript and for his helpful criticism.

SUMARIO Español

1. El propósito de este trabajo ha sido sostener la tesis de que la "purpura trombótica trombocitopénica" resulta del daño primario a las arterias y capilares y por lo tanto es una "enfermedad difusa vascular."

2. La evolución de la literatura sobre este tema ha sido trazada y un repaso de los aspectos clínicos, de laboratorio y de terapéutica de la enfermedad se ofrece. En cuanto concierne al desarrollo histórico del tema, se le ha dado especial énfasis a las observaciones de Orbison, Meacham y Allen, que sugieren que el daño principal a las porciones terminales del sistema vascular en muchos órganos es el proceso patológico esencial.

3. Un caso observado por el autor se discute en detalle. De este material secciones representativas se emplean para ilustrar la histogenesis de la lesión del primer estado de necrosis intramural vascular al "trombo blando" completamente desarrollado y propagado.

4. Aunque ningún "factor" de globulina anormal ha sido aislado en la enfermedad algunas de las características clínicas y hematológicas sugieren que está relacionada a enfermedades como la anemia hemolítica adquirida, purpura trombocitopénica y el lupus eritematoso diseminado, en las cuales se han demostrado mecanismos anormales inmunológicos.

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The Diffuse Vascular Lesion of So-Called "Thrombotic Thrombocytopenic Purpura"
HAROLD W. MARCH

Circulation. 1954;10:43-55
doi: 10.1161/01.CIR.10.1.43
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1954 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/10/1/43

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