THE ROLE OF ALLERGY IN THE PATHOGENESIS OF PURPURA AND THROMBOCYTOPENIA

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Allergy by one term or another has been recognized as an etiologic factor in purpura since the earliest descriptions of that disease. Until very recently, however, the intangible nature of both allergy and purpura, the multiplicity of potential etiologic factors, and the lack of exact knowledge of the pathologic changes in the latter state have made determination of the relative importance of allergy virtually impossible. Even now it is very difficult to evaluate the role of the allergic mechanism with accuracy. To attempt such an evaluation, it is essential to review briefly the chronologic development of the knowledge of the existence of allergic factors in the pathogenesis of purpura. It is likewise essential to define terms, for, as Piney1 has recently stated, "Among the confused chapters in hematology, purpura is the most confused."

For a number of years it has been our custom to use the term purpura to indicate vascular changes only.2 These vascular changes are characterized by reversible alterations of as yet unknown character in the walls of the smaller vascular radicles which make possible the escape of whole blood from the vascular bed. Such escape may occur more or less spontaneously (petechiae, nontraumatic ecchymoses) or it may be induced by increasing the intravascular pressure (e.g., "tourniquet test,"1 Göthlin test,1 etc.) or by decreasing the extravascular pressure ("suction test,"6 capillary resistometer,6 etc.). Artificial induction of petechiae is the most satisfactory criterion for the diagnosis of purpura at the present time, although lack of standardization of technics and variability of the vascular changes have made interpretation somewhat difficult. Other tests7,8 are more complex and less suited to routine clinical use, but are useful for supplementary or corroborative purposes. After comparative trial of the various tests, we have come to rely almost entirely upon a simple "tourniquet test" done with a pneumatic arm band at 100 mm. of mercury (unless the systolic pressure is below that level, in which case it is correspondingly reduced) and maintained for 8 minutes, unless extravasation of blood is so marked as to cause excessive infiltration of cutaneous tissues, in which case it is stopped at a shorter time. A representative area 2.5 cm. in diameter is chosen, and the petechiae in it are either counted or recorded graphically. More than ten easily seen petechiae within the circle is regarded as a positive test, and the petechiae in excess of that number may be regarded as a quantitative expression of the test. A positive test is interpreted to indicate the presence of purpura, but a single negative test is not adequate to rule it out because of the variable nature of the vascular changes.

Purpura in this sense may and does most frequently exist alone.2 It may, however, coexist with or be complicated by defects in the coagulation or clot retraction mechanism of the blood (hypoprothrombinemia, thromboplastin deficiency, thrombocytopenia, fibrinogenopenia) in which cases the combination of inadequate blood coagulation and "leaky" vascular walls produces an hemostatic error of such magnitude as to cause serious blood loss. From a clinical standpoint, it would seem to be much simpler to separate the vascular and hematologic factors and, at least for the purpose of etiologic studies, to consider thrombocytopenic purpura as purpura with thrombocytopenia or as two coexisting abnormalities. The im-

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One of the earliest discussions of the etiologic factors in vascular purpura is to be found in the "Opera Omnia" of Riverius. According to the English translation of Culpeper (1678), he stated: "But there is one Symptome proper and peculiar to a pestilential feaver which doth not happen in other Feavers; viz, Purple Specks or Spots on the whole body . . . which the Italian Physicians name Peticulae or Petechiae; and these Feavers which have these symptoms are commonly named Purpuratae or Petechiales . . . and sometimes they are very large and possess whole members . . . and then the parts appear tainted with redness which in a few hours oftentimes vanisheth away, and then returns again . . . and are commonly called Ebullitions of the blood . . . There do appear in other Diseases, spots very like unto those aforesaid, but springing from a far different cause; viz., from the over thinness of the blood, which being exagitated by the heat or the expulsive faculty does sprout forth of the Capillary Veins into the Skin. These spots are wont for the most part to appear in such as have some Flux of the Blood, because the Blood in such is more thin and watery: and also in Splenetic persons, and in such as have the Jaundice and old obstructions of the Bowels, and in all such . . . who are apt to fall into a Cachexy." Interpreted in modern terms, Riverius suggested that infections, blood diseases, malignancy, diseases associated with splenomegaly, jaundice and cachexia were of etiologic importance in purpura. The reference to the "redness which in a few hours oftentimes vanisheth away, and then returns again" may well be construed to represent the earliest recognition of an etiologic mechanism which might now be regarded as of allergic nature.

The next important addition to the list of causative or associated factors came a hundred years later when Werlhof in 1735 described the classical case of an "adult girl, robust, without manifest cause, attacked toward the period of her menses with a sudden severe hemorrhage from the nose . . . and about the neck and on the arms, spots partly black, partly violaceous or purple." It is well to recall that no knowledge of thrombocytopenia or other coagulation defect existed in the eighteenth century but, regardless of the presence or absence of such defect, this would seem to be the first recognition of endocrine factors in the etiology of purpura. In the same period Hornung suggested that clinical purpuras be divided into simplex, febrile and scorbutic types, thus apparently recognizing in his third group what we now know to be deficiency states as important etiologic factors.

The most tangible early suggestion of the relationship of allergy to purpura is found in the classification of Willan (1808) which included five types: purpura contagiosa, purpura simplex, purpura senilis, purpura hemorrhagica and purpura urticans. It is of interest to note that this classification may have been the origin of the term purpura hemorrhagica which has continued in general usage to the present time. A few years later Schönlein (1837) reported the symptom complex which has borne his name and in which purpura occurred in association with multiple joint involvement. The recent report of Montgomery of the incidence of purpura in rheumatic fever has re-emphasized the importance of this symptom group. In 1868 Henoch described a similar case and recorded the addition of severe ab-
dominal pain and intestinal hemorrhage. Six years later he added several similar cases and the syndrome characterized by purpura and abdominal pain has since borne his name. Many years later Glanzmann, in reviewing these syndromes, suggested that the basic mechanism in all of the cases of both the Schönlein and the Henoch types was of allergic nature and suggested that they be termed "anaphylactoid purpura," a view which has been almost universally accepted. The clinical reports of Osler, and more recently of Eyermann and others, have firmly established the importance of the allergic mechanism as an etiologic factor in a considerable portion of the cases of simple purpura without coagulation defect. It is interesting to note that in 1914 Osler stated that "perhaps the anaphylactic key will unlock the mysteries of the purpuras."

Thus by the middle of the nineteenth century the multiplicity of etiologic factors in purpura was well recognized. It was known that it might occur as a result of or in association with a varied group of clinical states including infections, diseases of the blood, malignancies, cachexia, endocrine disturbances, deficiency states in addition to gastro-intestinal, skin and rheumatic syndromes that are now regarded as of allergic nature. Clinical reports and experience since that time have confirmed amply the existence of all of these factors, and in recent years have emphasized the importance of the allergic group.

Until the latter part of the nineteenth century, purpura was considered simply as a vascular disease because of the paucity of knowledge of blood coagulation defects. There had been no knowledge of the existence of blood platelets until the studies of Donné (1842) suggested the presence of a third cellular substance in the blood. Hayem confirmed these studies in 1878 and Bizzozero completely established the identity of blood platelets in 1881. Brohm (1881), Denys (1887) and Hayem (1895) soon discovered the fact that the blood platelets were sharply reduced in some cases of purpura though not in all.

In the decade or two which followed the discovery of the relation of platelet reduction to purpura, profound changes occurred in the interpretation of the disease. Attention was focused primarily on the platelet reduction, and clinical cases were divided into thrombocytopenic and nonthrombocytopenic types with subdivision into secondary and primary groups depending upon whether or not they were associated with recognizable clinical disease. Partly because of its dramatic clinical manifestations, and partly because of the absence of tangible etiologic clues, "primary thrombocytopenic purpura" quickly occupied the center of attention and has retained that position to the present time. Numerous synonyms have developed, including essential and idiopathic thrombocytopenic purpura and Morbus maculosis Werlhofii, with varying appropriateness. It is important to recall also that, prior to the time when the concept of primary thrombocytopenic purpura came into existence, it was impossible to differentiate severe purpura from hemophilia, hypoprothrombinemia and fibrinogenopenia as we know them today. Consequently it is not surprising that thrombocytopenic purpura, with its severe and often lethal blood loss, should have been grouped with these diseases under the general title of "hemorrhagic diseases" and more or less separated from its closer allies, the nonthrombocytopenic or "simple" purpuras. This confusion was rela-
tively short-lived however and was cleared by the development of practical methods for the enumeration of platelets, demonstration of the lack of syneresis in thrombocytopenic purpura (Hayem),

development of satisfactory methods for determination of coagulation time, development of the tests for bleeding time (Duke) and prothrombin time (Quick), and the clinical observations of Hayem, Minot, Duke, and many others.

The pathogenesis of the thrombocytopenia which was found in the last decade of the nineteenth century to occur so frequently in association with purpura has been the subject of many experimental and clinical studies since that time, although a few workers have maintained interest in the vascular phases of the disease, and a still smaller number have steadfastly persisted in efforts to correlate the vascular and hematologic phases. Hayem suggested that the reduction of platelets was due to decreased production or increased destruction of those elements, but since the origin and fate of the platelets were still unknown at that time he was unable to throw any light on either mechanism. Significantly, however, he did suggest the possibility of an allergic factor in the latter mechanism by demonstrating the reduction of platelets in "anaphylactic" states after peptone injection, and with heterologous serum. He also demonstrated platelet reduction in severe infections. It was during this period, apparently, that the concept of the vascular changes being due to the platelet reduction gained favor, a concept which contributed much to the confusion of the subsequent years. Hayem’s experimental work with heterologous serum doubtless provided the background for the tremendous interest in the reduction of platelets by the use of antiplatelet sera which was studied by many observers during the early part of the twentieth century and which demonstrated beyond question the susceptibility of the platelets to antiplatelet substances of biologic origin.

It was also during this period that the origin of the platelets in the megakaryocytes of the bone marrow was established by Wright and corroborated by Bunting and by Downey. This observation provided a valuable clue to the mechanism by which platelet reduction might occur as a result of decreased production, and it was soon established by Duke, Minor, and others that platelet deficiency did occur in bone marrow diseases such as leukemia and aplastic anemia. Duke also confirmed the reduction of platelets in severe infections, notably diphtheria and tuberculosis, after peptone injection, after massive x-ray irradiation (Heineke), demonstrated reduction by chemical toxins of the benzol type and, most importantly from the allergic standpoint, showed experimentally the reduction of platelets as a result of a hypersensitivity mechanism in rabbits sensitized to horse serum. Except for our present incomplete knowledge of deficiency of maturation factors and the role of the spleen, the etiologic background of thrombocytopenia was as complete in theory at that time as it is today. Myelopathy, severe infection and toxemia, chemical intoxication, x-ray irradiation, and allergic reaction had been established as important mechanisms capable of causing a reduction of platelets in the peripheral blood.

It was at that point that the tremendously important role of the spleen in platelet reduction was discovered more or less by chance. Kaznelson demonstrated, and
many others have amply confirmed, prompt and dramatic increase of the circulating platelets following splenectomy in certain cases of thrombocytopenia. Interestingly, Elliott has also demonstrated prompt reversal of the vascular changes following splenectomy in cases of purpura with thrombocytopenia. In the intervening thirty years splenectomy has been established as the standard therapeutic approach to cases of "primary" or "idiopathic" thrombocytopenic purpura, and has been shown to be particularly effective in those instances in which there is an ample number of megakaryocytes in the bone marrow. In spite of that position in therapy, however, removal of the spleen still remains a somewhat empiric procedure, for the mechanism by which it influences the level of the platelets in the circulating blood has never been clarified. There is still uncertainty and controversy as to whether the spleen destroys the platelets, inhibits their development in the bone marrow, or controls their release from the marrow, and what relation if any it bears to the allergic mechanism which seems to bear close resemblance to splenic action clinically.

Unfortunately, methods for the clinical study of the allergic mechanism in the production of thrombocytopenia, which has been so convincingly demonstrated experimentally, have been relatively unsatisfactory. However thrombocytopenia with purpura following ingestion of various drugs has been reported by Loewy, Peshkin and Miller and others, and thrombocytopenia has been produced at will in some of those patients by readministration of the offending drug and by skin testing, thus establishing the reaction as of allergic type. Further, demonstration of the allergic mechanism responsible for the granulopenia in agranulocytic anemia, and of the fact that sensitivity could be detected in those instances by granulocytic response following ingestion of the offending allergens, has suggested that platelets might behave in a similar manner and has corroborated the soundness of the "ingestion" method of demonstrating thrombocytopenic response to allergenic substances. Utilizing that method of testing in addition to the usual allergic diagnostic methods, it has been increasingly possible in recent years to establish allergic reactions as one of the causes of clinical thrombocytopenia with or without purpura. Squier and Madison and others have shown that allergenic foods are capable of producing thrombocytopenia by demonstrating platelet reduction following ingestion of those foods, and have shown return of the platelet count to normal levels after the removal of the foods from the diet with clinical recovery.

Thus it is evident that in the evolution of knowledge of etiologic factors in thrombocytopenia and in purpura, allergy has been established as one of several factors capable of producing thrombocytopenia and likewise as one of several similar factors that are capable of producing the vascular changes characteristic of purpura. The curious similarity of these etiologic factors may well explain why purpura occurs so much more frequently in association with thrombocytopenia than with hypoprothrombinemia or thromboplastin deficiency. In the case of the allergic factor it is readily conceivable that an allergic individual might have both hematologic and vascular response simultaneously and to the same allergen, producing typical "thrombocytopenic purpura." Clinical evidence to support this possibility is accumulating slowly, and is derived principally from satisfactory
clinical response of both thrombocytopenia and purpura to allergic control without splenectomy. With advances in the technic of allergic studies, and with wider use of the ingestion method of testing, it is likely that more cases will be found to fall into the allergic category and to respond favorably to that method of therapeutic approach.

SUMMARY

It has been suggested that, for purposes of etiologic investigation, thrombocytopenic purpura be separated into its two component parts, thrombocytopenia and purpura, and that they be regarded as two coexisting abnormalities rather than as a single disease. Historical review of the development of knowledge of the pathogenesis of purpura emphasizes the importance and soundness of this dual approach. Both thrombocytopenia and purpura have been shown to have a complex etiologic pattern with multiple potential etiologic factors. The curious similarity of these two groups of factors may at least partially explain the frequent coexistence of the two abnormalities in the clinical picture of thrombocytopenic purpura.

It has been shown that allergy has long been recognized as an etiologic factor of major importance in both purpura and thrombocytopenia. It is logical, therefore, that it should frequently be an important etiologic factor when the two conditions exist together, and it is suggested that when diagnostic methods are more adequate a considerable number of cases of "idiopathic" thrombocytopenic purpura will fall into that category and will yield therapeutically to a proper allergic approach.

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