Autoerythrocyte Sensitization or Psychogenic Purpura?

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The following report describes the occurrence, in four women, of an abnormal response to bruising, characterized by local pain, swelling and extension of bleeding into adjacent areas, often to a serious extent. The histories and laboratory investigations suggest that, in these patients, there has occurred a sensitization against one of their own body tissues, namely red blood cells.

The above quotation is taken from the original clinical report in which Gardner and Diamond (1955) described the syndrome of autoerythrocyte sensitization as an unusual purpuric syndrome in which crops of apparently spontaneous painful inflammatory ecchymoses occurred in four women who had sustained physical injury shortly before the onset of symptoms. They postulated that, as a result, their patients had become sensitized to their own erythrocytes and, subsequently, extravasation of blood during the unrecognized trivial injuries of everyday life induced the purpuric lesions. As predicted by this hypothesis, Gardner and Diamond could reproduce the typical bruises of autoerythrocyte sensitization by the intracutaneous injection of the patient's own blood. The offending agent appeared to be erythrocytic stroma; neither plasma, white cells nor hemoglobin elicited a response. One patient was found to be sensitive to the phosphatidyl serine of the red cell membrane (Groch, 1966). Since that time approximately 50 patients have been reported, most of whom were reviewed by Ratnoff and Agle (1968); Hersle and Mobacken (1969).

Gardner and Diamond (1955) postulated that fixed tissue antibody reacts with the red cell stroma to produce edema, increased capillary permeability, and extravasation of red cells into tissues.

As further patients with this syndrome were reported it became clear that in some otherwise typical cases the cutaneous response to blood might be consistently negative. Further doubt that the syndrome may have anything to do with autoimmunity is raised by a thorough study by Ratnoff and Agle (1968) of 27 women with the characteristic bruising. In nine patients the lesions could not be reproduced by the intracutaneous injection of autologous blood. All the patients had severe emotional disorders and the repetitious nature of their psychiatric problems suggested that emotional factors might be critical in pathogenesis. Although symptoms first appeared after physical injury or surgery in 19 of the 27 patients, a closer correlation could be obtained between severe emotional distress and the onset or exacerbation of purpura. A similar association was noted by McDuffie and McGuire (1965). In the experience of these workers and of others, symptoms of purpura usually appeared during the third and fourth decades of life. All known cases of this disorder have been in women.

Many attempts have been made to demonstrate the presence of antibodies directed against red blood cells in patients with autoerythrocyte sensitization. Gardner and Diamond (1955) found that their patients' red cells would not react with antihuman globulin antiserum, and studies for plasma hemolysins and agglutinins against erythrocytes were negative. These findings have been repeatedly confirmed. It has not been possible to demonstrate skin-sensitizing antibodies to blood or its constituents in serum by the Prausnitz-Kustner technique (Gottlieb, 1957; Kremer, 1967). Ratnoff and Agle (1968) were unable to detect antibodies in their patients' serums by hemagglutination of tanned red cells coated with stroma. These various negative studies make it unlikely that the patients have an immunologic sensitivity to blood,

stroma, or hemoglobin. They do not preclude the possibility that in these individuals the threshold of reactivity of the blood vessels to noxious stimuli has been lowered by nonimmunologic means. Agle and Ratnoff (1962) reviewed the evidence that the reactivity of the skin to histamine or thermal injury can be influenced by suggestion. The observation that the appearance of new ecchymoses in patients with autoerythrocyte sensitization is affected by emotional stresses may mean that the reactivity of blood vessels to stimuli is influenced by the central nervous system. This view is fortified by studies of the effects of hypnotic suggestion (Agle and Ratnoff, 1967). The possibility that psychological factors were directly concerned in the purpura was suggested by studies in some of the 27 patients in whom injection of either blood or normal saline into the skin of the anterior thigh each induced typical purpuric lesions. However, if injections were made on the posterior thigh and the sites covered so patients were unable to see them, either no lesions were produced or purpura occured at the saline injected sites only. The strong influence of the psyche was further documented when hypnotic suggestion was found to suppress reactivity to blood in a patient previously reactive, and vice versa (Caron, 1969).

The evolution of the cutaneous bruises is remarkable in that an inflammatory component differentiated the ecchymoses from those associated with injury or hemostatic defects. Usually the patient's attention was drawn to a fresh lesion by a subjective sensation described as stabbing, burning, tingling, cramping, throbbing, popping, or painful. The subjective prodromata constitute a central and diagnostic feature of autotrythrocyte sensitization. Either immediately, or within an hour or two, the patients became aware of erythema or puffiness at the site of the subjective sensation. Ecchymoses only became prominent several hours or a day after the subjective sensations, swelling, and erythema had been noticed. In some patients:

> An ecchymosis began as a ring around the central erythematous area, giving the appearance of a target, while in others, it was more often superimposed upon the erythematous region. In either case, the blue area usually spread rapidly for a distance of several centimeters around the zone originally affected. After a day or two, the swelling and erythema subsided, and the ecchymosis began to involute, disappearing in a week or two. Severe ecchymoses often had a mottled appearance, in which the areas around the hair follicles were more intensely blue than the regions between, a phenomenon seen in normal individuals who have been bruised. Although typical bruises were tender a day or two, pain often subsided more quickly, sometimes as soon as the patient was aware that the spots had turned blue. The bruises varied in diameter from a centimeter or two to 15 cm or more, encompassing, for example, most of the forearm of calf, although such large lesions were seen in only a few cases (Ratnoff and Agle, 1968).

Pain and tenderness were common findings in all patients (Ratnoff and Agle, 1968). Bruising occurred most often in the skin of the lower extremities, particularly the anterior and lateral thighs and legs. The frequency with which the patients or their families related flare-ups of cutaneous purpura to emotional tensions was notable; the relationship was clearly demonstrable in 19 of the 27 patients studied (Table). Biopsy of the early lesions when the affected area appeared erythematous, swollen, and warm revealed edema in the upper dermis; the capillaries of the dermis or subcutaneous tissues were surrounded by an infiltrate of mononuclear cells, most of which were small lymphocytes. Later, extravasated blood cells were evident. It should be mentioned at this point that all patients in Ratnoff and Agle's study (1968) underwent thorough examinations of their hemostatic mechanisms (including clotting times, prothrombin time, partial thromboplastin time, platelet count, bleeding time and clot retraction, as well as the agglutinating effect of ADP upon the patients' platelets) with uniformly negative results. Likewise, lupus erythematosus cell tests, antinuclear antibody, and serum electrophoresis were always negative. None of the patients had evidence of hemolytic anemia.

As mentioned previously, the syndrome is confined to adult women who usually have multiple systemic complaints. Prominent among these are severe headache; transient paresthesias; transient paresis; repeated syncope; diplopia; abdominal pain or distress; nausea; vomiting or diarrhea; chest pain; dyspnea; dysuria; frequency of urination; hematuria; menorrhagia; epistaxis; gastrointestinal hemorrhage; joint, muscle or back aches; and remarkable fluctuations of body weight. No organic cause was found for most of the patients' symptoms.

Extensive psychologic evaluation of all 27 patients was carried out with a remarkable uniformity of findings. Five components in the psychologic make-up of patients with this syndrome were almost always present: hysterical and masochistic character traits, problems in dealing with their own hostilities, and overt symptoms of depression and anxiety. Sixteen of the 27 patients had had psychiatric evaluation or care at some time during the years before the onset of purpura. The masochistic nature of the patients' personalities invariably suggested the possibility that their bruising was self induced. And, in fact, several patients in many different studies have been noted to induce

TABLE

Clinical Features of Autoerythrocyte Sensitization in 27 Patients

(Based on data from Ratnoff and Agle, *Medicine* 47 : 475, 1968)

Feature	Number of Patients (Total = 27)
Female	27
Age at Onset of Purpura	
31–40 years	10
21–30 years	8
14–20 years	4
41–50 years	4
51 years	1
Precipitating Factors in Production of Skin Lesions	
Injury	11
Surgical procedure	9
Emotional stress	23
Skin Lesions (in order of appearance)	
Preceded by subjective sensation (stabbing, burning, tingling, cramping, etc.)	27
Erythema and/or Puffiness	27
Tenderness and/or Pain	27
Ecchymosis	27
Distribution of Skin Lesions	
Legs	27
Arms and Wrists	20
Abdomen	10
Breasts	7
Face	8
Back	3
Skin Test Results (using intracutaneous injection autologous blood)	
Positive (ie, reproduction of characteristic skin lesion)	18
Negative (no response)	9
Emotional Characteristics of Patients with AES	
Depression	20
Suicidal attempt	5
Overt sexual problems	18
Hostility	15
Masochism or martyrism	15
Anxiety	14
"Hysteria"	14
Emotional lability	11

new lesions factitiously. Nevertheless, not all of the lesions are factitial.

DNA autosensitivity somewhat resembles autoerythrocyte sensitization but may be a different disorder (Chandler and Nalbandian, 1966). Spiera and Schwartz (1970) present a patient with the typical syndrome of autoerythrocyte sensitization including recurrent painful ecchymoses and a severe psychiatric disorder. Her lesions could be reproduced by subcutaneous injection of both autologous red cells and heterologous DNA. Other authors (Levin and Pinkus, 1961) feel that these two entities should be differentiated, since patients with DNA autosensitivity improve when given chloroquine; but no treatment including splenectomy, antimalarials, steroids, antihistamines, ethinyl-estradiol, anticoagulants, antibiotics, 6-MP, or vitamin C has been successful in patients with autoerythrocyte sensitization syndrome (Khan and Cash, 1970). The possible relationship between DNA sensitivity and autoerythrocyte sensitization remains unsettled (Ratnoff and Agle, 1968).

Therapy in this disorder, as outlined by McDuffie and McGuire (1965), should be limited to provision of emotional support, encouragement, and the lessening of environmental stresses. This, then, is a recommendation for "supportive psychotherapy."

> Long-term somatic treatment and investigations of physical complaints in which psychic factors are prominent rapidly fix the problem at a physical level and make more and more inaccessible the emotional antecedent. Accordingly, we recommend early diagnosis, a recognition and consideration of emotional antecedents that may be present, and resistance against the use of somatic therapy (Ratnoff and Agle, 1968).

The prognosis of autoerythrocyte sensitization is difficult to determine because of the fluctuating nature of the symptoms. Of the 27 patients studied, 10 had ecchymoses for 10 years, and one as long as 20 years. The severity of bruising varied from time to time. A decline in the severity of bruising or remission has occurred in at least eight cases (Ratnoff and Agle, 1968). Although the purpura often appeared to improve with the years, this change was not accompanied by an amelioration of the patients' multiple somatic complaints, which in most cases continued without let.

The studies of Ratnoff and Agle (1968), the most extensive studies done on this disorder, are consistent with the hypothesis that in patients with autoerythrocyte sensitization the purpuric lesions are related to emotional stresses. The mechanisms through which these stresses are translated to cutaneous bruising are unknown. A factitious origin for the patients' ecchymoses cannot be rigidly excluded, but this possibility seems inadequate to explain the symptom complex

observed. These authors postulate that the purpuric state observed may be an hysterical conversion reaction mediated through the autonomic nervous system and, therefore, that the term psychogenic purpura may be more appropriate than autoerythrocyte sensitization.

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