Autoerythrocyte Sensitization

A Form of Purpura Producing Painful Bruising Following Autosensitization to Red Blood Cells in Certain Women

By Frank H. Gardner and Louis K. Diamond

It is generally known that some women bruise easily and develop ecchymoses particularly in the lower extremities, without definite trauma. Studies of the blood clotting factors in such individuals have yielded normal or equivocal results. This vague hemorrhagic diathesis has been called "purpura simplex" and described as consisting merely of easy bruising and bleeding into the skin and subcutaneous tissues. It is usually only a source of minor annoyance to the subject, and otherwise of little significance.

In contrast to this, 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 clinical histories of these four women are presented to describe this disorder. The methods of investigation and results are outlined to demonstrate the abnormal tissue response associated with sensitization to red blood cells.

Case I (L. A.), is a 44 year old nurse who, twenty years before admission to the Peter Bent Brigham Hospital, had been struck by an automobile, and had suffered a fracture of the skull with concussion, and a fracture of the pelvis, with multiple abrasions, contusions and ecchymoses of the lower extremities. Two months later her physician observed that her right knee remained stiff and had a persistent ecchymotic area. The knee joint was explored surgically and a hematoma removed from the patellar bursa. However, the ecchymotic areas around the knee continued, and the patient began to have painful swelling and ecchymoses around the ankle. At this time, she was seen by one of us (L. K. D.) and had many blood studies performed, all of which yielded no abnormal results. During the next year she had numerous episodes in which painful ecchymotic areas developed over the extremities. Bleeding and clotting times, capillary fragility, blood platelet counts, and prothrombin concentration tests were within normal limits. In 1939, seven years after the accident, the patient had an episode of hematemesis, which was followed shortly by a cerebral hemorrhage. A right hemiparesis developed from this but disappeared after several months. Although she had melena intermittently for three months, no lesion in the gastrointestinal tract could be demonstrated by fluoroscopic studies. Throughout the seven year period following her automobile accident she continued to have painful ecchymotic lesions.

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The authors wish to acknowledge the kindness and assistance of Dr. Elizabeth Broyles, of Wellesley, who first referred cases II and III to one of us (L. K. D.) and carried out some of the treatment suggested.
These studies indicated an abnormal response to the patient has had progressive increase in the number of her painful ecchymotic areas. and appeared to be controlled by an injection of whole blood. During the past two years these were thought to be characteristic of Raynaud's syndrome. In April 1940, a right cervical sympathectomy was done on the advice of several hematologists, in the hope of diminishing her hemorrhagic episodes. For three years following splenectomy the patient had no painful ecchymotic areas. Also, her episodes of painful skin hemorrhages were never as severe after her splenectomy. In 1948 the patient had some disturbance of vision in the left eye and was found to have a dilated left pupil. A neurologic consultant believed that the patient had a minor cerebral hemorrhage and the lesion resolved over a two month period.

In 1948, three years before entry to this hospital, the patient had a severe episode of diffuse subcutaneous bleeding that she could not associate with any trauma. These lesions were terminated by two 10 cc. injections of whole blood intramuscularly. At this time she took Rutin for several months without noticeable effect. The patient had many episodes of painful bruises precipitated by dental extractions. It was found that 10 cc. of whole blood, given intramuscularly before extraction, would diminish the severity of the ecchymoses.

In the early part of 1950 the patient developed vasomotor changes in the right hand. These were thought to be characteristic of Raynaud's syndrome. In April 1950, a right cervical sympathectomy was done with an excellent resulting control of the vasomotor instability. Eight hours following the surgery the patient had painful hematoma on both thighs, over her anterior ribs and in both arms. These lesions did not increase in size and appeared to be controlled by an injection of whole blood. During the past two years the patient has had progressive increase in the number of her painful ecchymotic areas.

The physical examination on entry to this Clinic in 1951 was unremarkable. No residual abnormalities of the skin were observed or palpated despite the numerous ecchymotic lesions during the previous twenty year period. Laboratory examination revealed that bleeding and clotting times, plasma prothrombin concentration, serum prothrombin consumption, and platelet counts were all normal. Other laboratory studies were not remarkable. During the period of hospitalization, certain skin tests were done as noted below. These studies indicated an abnormal response to high concentrations of red blood cells as well as to red cell stroma. While being given these tests she had a marked exacerbation of her disease with the appearance of painful ecchymotic areas, which developed on her anterior hips and thighs and over the back. It would appear that these lesions were associated with pressure points while she was in bed (Fig. 1). They were painful and characteristic of her previous lesions. The patient stated that she could tell when an ecchymotic lesion was about to appear. The area involved became painful and a distinct induration of the skin could be felt. The skin was warm and tender to palpation. Within 12 to 24 hours a dusky violaceous mottling developed in the center of the lesion followed by progressive ecchymoses.

Inasmuch as the patient had to return to her home in a distant city, she was given 150 mg. of cortisone acetate per day for a five day period. Although the lesions were not observed, the patient reported by letter that they resolved more quickly and were less painful than she had noted in previous episodes. Since that time, the patient has used cortisone...
acetate by mouth to control the pain of the ecchymoses and to decrease the time interval required for resolution of the lesions.

Comment: This patient has the longest history of the four women studied. Her initial lesions were associated with wide-spread trauma following an automobile accident. A wide variety of medical treatments were ineffective. A splenectomy was done in an effort to improve the bleeding tendency and to control the ecchymotic lesions. Following splenectomy the skin lesions were absent for a three year period, but then reappeared.

Associated with the skin lesions, the patient has had two episodes of cerebral hemorrhage, and repeated bleeding from the gastro-intestinal and genito-urinary tracts without known trauma. There is no history or physical findings to suggest familial telangiectasia. Finally, the patient has had vasomotor changes in the right hand requiring sympathectomy for relief. These multiple symptoms would suggest that the patient may have a diffuse vascular defect as well as an abnormal tissue response to extravasated red cells. During the first fifteen years of the patient's illness, her painful ecchymotic lesions were initiated by trauma. In later years, "physiologic trauma" appears to have been adequate to initiate the abnormal tissue reaction. The use of whole blood injections to control the painful lesions is of interest, for certainly one would anticipate further sensitization from the procedure, but some "desensitization" and temporary benefit seemed to result.

Case II (E. B.), is a 33 year old housewife. In 1939, at the age of 19, a window seat fell on the dorsum of her left wrist. It became ecchymotic and the hand remained swollen for
three months. Because of persistent pain, the wrist was explored surgically and normal fluid was found in the bursal sac. For several years following this episode, the patient had attacks of syncope which were carefully investigated without adequate explanation. During one of these she bruised her ankle, and during the next week, a painful ecchymosis extended to her knee. She was admitted to the Peter Bent Brigham Hospital in 1940 to determine the cause of her bruising tendency and syncope. Physical examination and laboratory studies were noncontributory. Bleeding and clotting times, capillary fragility, platelet counts, and prothrombin concentration were within normal range. One year later the patient bruised her right hand, and during the subsequent week there was a progressive painful hematoma over the wrist, followed by painful ecchymoses that extended up her arm to the deltoid area. The patient was given intramuscular injections of whole blood without response.

One month later a splenectomy was done in this hospital without complication. The spleen had no abnormal histologic findings. Subsequent notes in the hospital record state that the patient was relatively free of painful ecchymoses for eight months after splenectomy. However, the patient does not believe that splenectomy altered the incidence of lesions at that time. During the next year she had progressive painful ecchymosis following any minor bruise. She was given frequent injections of red cell extract* but this therapy did not alter her response to bruising. When in six months after these injections were started the patient was given 0.2 ml. of the red cell extract in the left arm, there followed a painful ecchymotic reaction extending over the entire left arm. The red cell suspension was discontinued after this reaction. In 1944, two years later, she bruised her right forearm and the ecchymotic area slowly spread to her shoulder. By 1947, the patient commented that her response to bruising had changed so that minor trauma was not associated with extension of the ecchymoses although the immediate area was quite painful.

In 1947 the patient had a transient episode of painful joints in the hands and elbows that was thought to be rheumatoid arthritis. Small tonsillar tabs were removed surgically with marked improvement in her arthritis. Thereafter, her abnormal response to bruising tended to diminish, according to the patient, although during 1948 she had one episode of bruising with slight extension of a painful ecchymotic area on the right arm. No painful ecchymotic areas appeared following bruising during the past seven years.

Only limited studies could be done when this patient was seen in the Out-Patient Medical Clinic in 1952. As is noted below, she still showed an abnormal response to the intradermal tests with red blood cells and red cell stroma.

In 1954, the patient had a normal uneventful first pregnancy ending in the easy delivery of a fine healthy boy. There were no postpartum complications or bleeding.

Comment: This patient had a prolonged response to injury and hemorrhage but in contrast to cases I and IV, she has never had spontaneous ecchymoses develop elsewhere than in areas of trauma. Although some observers felt the patient showed improvement following splenectomy, she herself stated that she could not notice any diminution in frequency of the painful ecchymoses as a result of trauma. After about nine years of such episodes, she became relatively free of painful ecchymoses and has been well for the past six years.

Case III (R. G.), a 19 year old college student, in 1950, fell on the stairs in her school dormitory. This resulted in a painful swelling of the right wrist with a large ecchymosis, but no fracture. During the next three weeks the ecchymosis gradually spread to cover the entire right forearm and upper arm, and was associated with tenderness and edema. Over a period of another month the lesion slowly subsided. Four months later, the patient hit her left knee on a door. A large painful ecchymotic area promptly developed and persisted for a week. She was first seen by one of us (L. K. D.) six months after the initial

* The blood clot extract was made from clotted whole blood. After retraction, the clotted red cells were removed and dried. The dried red cell mass was steriley suspended in saline solution in a 1:10 dilution and agitated to make an even suspension. Initially, 0.05 ml. of the extract was given subcutaneously at weekly intervals.
trauma and referred to this Clinic because of a painful ecchymosis at the site of a venipuncture in her right arm. On admission additional history and her physical examination were not remarkable. She was a large, obese girl, which made palpation of abdominal organs difficult. Laboratory studies at this time were within normal limits including bleeding and clotting times, plasma prothrombin concentration, serum prothrombin consumption, blood platelets, and clot retraction. During a period of hospitalization, studies demonstrated an intradermal sensitivity to red cells and red cell stroma as will be described below. After a second series of intradermal tests with blood from a normal donor, the patient had the onset of transient left upper quadrant pain which had never been noted with previous ecchymotic lesions.

In view of the patient’s tissue response to red blood cells, a preparation of red cell stroma (50 per cent hematocrit concentration) was made, in order to carry out a “desensitization” program. This was started by her school physician in a dosage of 0.01 ml. intradermally per day. When this dosage was gradually increased to 0.04 ml. per day, the patient developed a painful area of erythema, 3 cm. in diameter, eight hours after injection, and within twenty-four hours this had become ecchymotic. Also, there was a transient episode of nausea and vomiting and left upper quadrant aching, but no splenomegaly was felt. The ecchymotic lesion extended slowly over the next seventy-two hours to cover a 15 cm. ovoid area. No further injections of red cell stroma were given.

Four months later, she hit her right thigh and subsequently developed only a small ecchymosis. However, during the next week the lateral surface of the right thigh became progressively swollen, painful and black and blue, as the lesion slowly spread to the level of her right knee. On the day after injury the patient complained of aching pain in the left upper quadrant, which was accentuated by motion or respiration. She had nausea and vomiting. Physical examination at this time revealed tenderness on deep palpation of the left upper quadrant. The lesion over her right thigh was tender, indurated and erythematous with an ecchymosis at the site of the initial trauma. Laboratory studies were not remarkably different from her previous examination. The patient was hospitalized for a three-week period primarily because of abdominal distress and for institution of parenteral fluid therapy. During the first week the painful lesion on her thigh resolved, but the abdominal distress continued for several weeks. Her spleen was never palpated although it was considered that she might have a splenitis. For two weeks an irregular intermittent fever was present but subsided as the ecchymoses disappeared.

Four months later the patient bruised her left calf while bicycle riding. This lesion slowly spread over the left leg and was associated with left upper quadrant pain and much vomiting. Again she was hospitalized for twelve days to receive needed parenteral fluids. Once more there was marked tenderness when the left upper quadrant area was palpated, but the spleen was not felt. During the following year the ecchymotic lesions were less severe and they were not associated with abdominal distress. The patient has not been seen for the past three years. However, she states, through correspondence, that she has had less reaction to bruising than when she was seen here initially. During this period she has had three attacks of thrombophlebitis associated with trauma to her legs and has been treated with anticoagulants. No further intradermal tests have been done to determine if the abnormal response to red cell stroma persists.

Comment: As was noted in the other patients, the initial painful ecchymoses followed an episode of trauma, and subcutaneous bleeding during which sensitization to red cells could develop. This patient also had associated left upper quadrant pain suggesting an acute splenitis. The abdominal distress was also accentuated or initiated by the intradermal injections of red cell stroma. Over a two-year period the patient gradually lost her abnormal response of sensitization to bruising. It is of interest to note the recurrent thrombophlebitis.

Case IV (I. B.), was a 60 year old housewife. In 1934, at the age of 43, this patient fell and injured her right foot, spine, and head. She was placed in a body cast and required to
stay in bed, at which time she developed a contracture in her right leg. It was at this time she began to notice for the first time painful ecchymoses on her lower extremities. In 1937 she had a cholecystectomy and, one year later, she had onset of nausea and vomiting and was operated on again, for intestinal obstruction. Subsequently, she has had many similar attacks which have been relieved by a gastric suction, abdominal hot packs, and enemas. The episodes of ecchymoses that began fifteen years ago were described by the patient as being preceded by a feeling of pain, heat and induration, followed by the appearance of a black-and-blue spot. These disappeared after one year and then reappeared two years ago (17 years after the first episode). They have persisted until she was first studied here in 1952. During the last two years before admission, the occurrence of areas of ecchymoses had become more frequent and painful. However, they were limited to the lower extremities. Although the patient thought that some lesions were associated with trauma, many occurred without known injury.

Seven years before entry she had had an episode of coma, associated with right hemiplegia. The hemiplegia improved after two weeks, although she has had some residual paralysis of the right facial nerve and a slight left hemiparesis. Four months before entry, in 1951, she had an episode of melena at which time transfusion with two pints of blood was required. This has not recurred since and no explanation could be found then for the bleeding.

The patient was admitted to the Peter Bent Brigham Hospital in 1951 for evaluation. Physical examination was not remarkable aside from the residual weakness from the old hemiplegia. Laboratory tests including plasma prothrombin concentration, serum prothrombin consumption, blood platelets, and fibrinogen levels, yielded normal results. Bleeding and clotting times were within normal limits, and the capillary fragility test was not remarkable.

Skin tests with concentrations of the patient's red cells were performed with results as noted below. During the period of study numerous intradermal tests were done on the upper extremities. Within a period of two months after the initiation of these studies the patient began to have painful ecchymotic areas over the upper extremities that had not existed prior to this. These were spontaneous and not associated with trauma, but for the most part were associated with lesions on the lower extremities.

Frequent injections of the patient's whole blood were given intradermally to determine if the ecchymotic response could be altered. At weekly intervals the patient received 0.1 cc. of whole blood in five areas of the thigh for a total of 0.5 cc. After one month of therapy, the patient began to complain of left upper quadrant pain within 48 hours of the injections. The sites of injection were tender, painful, and associated with erythema. The abdominal pain was accentuated by deep respiration and motion. The spleen was never palpably enlarged but in view of our experience with case III, the possibility of a splenitis was considered and therapy was discontinued. After a month had elapsed, the program of "desensitization" was re-started. Again, after the first course of injections, the left upper quadrant pain recurred. This was now associated with spontaneous painful ecchymoses over the other extremities. During the following three-month period, weekly intradermal injections were carried on, each time associated with varying degrees of abdominal distress. However, the interval of time between injection and onset of left upper quadrant pain became shorter until the patient began to experience abdominal pain within 6 to 8 hours after the intradermal test. During this period, the local reactions to the blood injections disappeared, and associated with the loss of skin reactions, her painful ecchymotic lesions ceased. The intradermal injections were discontinued after a three-month period because of the progressive abdominal distress. The painful ecchymotic lesions began to recur within these months. Although the patient had not had abdominal pain with her lesions before this study, she now experienced acute abdominal distress associated with nausea and vomiting for a forty-eight hour period with each new ecchymosis. The episodes of ecchymoses and abdominal pain persisted for the next six months. Because of abdominal distress splenectomy was considered. However, the uncertainty of the pathologic lesion and the equivocal response in the other two patients excluded this procedure. During the next year the ecchymotic lesions became less severe, although bruising was still associated
with extension of the lesion. Also, during this period abdominal distress following bruising disappeared. The patient states that her skin lesions have been less marked following the intradermal injections of whole blood. However, the episodes of left upper quadrant pain have not been explained and no further therapy has been given.

Comment: It was of interest that in this patient the lesions were limited to the lower extremities when she was first examined. Following numerous skin tests in the upper extremities, the same type of lesions developed there. The patient also has had a cerebral vascular accident and one episode of gastrointestinal bleeding. Associated with intradermal injections of red cells the patient had the onset of abdominal pain. There was suggestive evidence that repeated intradermal injections of whole blood decreased the painful ecchymotic response. Although these injections were initially associated with abdominal pain, the patient, over a period of a year, lost this response when the injections were stopped.

METHODS AND MATERIALS

Routine hematologic and laboratory studies were performed as outlined by Ham.1

Skin Test Materials and Procedures:*

1. Intradermal injections of red cells: Venous blood was collected with heparin as anticoagulant. After centrifugation the plasma was removed and saved. The red cells were washed thrice in physiologic saline and pipetted into 4 ml. hematocrit tubes. These tubes were centrifuged vigorously and saline was added to the tubes to prepare a series of red cell hematocrits ranging from approximately ten to eighty per cent concentration. The red cells were mixed well and small aliquots of the suspensions were aspirated into tuberculin syringes for intradermal injection.

2. Intradermal injections of plasma and serum: The plasma removed in the preparation of red cells was used. Serum was obtained from clotted blood. Also, clotted blood was allowed to incubate twenty-four hours at 37°C before the serum was removed. In a few instances, the Buffy coat of leukocytes and platelets was saved. This preparation was mixed with a small amount of plasma for intradermal injection.

Alpha, beta, and gamma globulin fractions were prepared from the plasma by the technique of Lever et al.2 Twenty-five per cent commercial human albumin solution was used instead of preparing such from the individual patient’s serum.

3. Intradermal injection of Stroma: Red cell stroma was prepared utilizing the technique of Howe.3 Sterile precautions were observed and each preparation was cultured to exclude bacterial contamination before it was used. One cc. of packed washed red cells were lysed by adding ten volumes of distilled water. 1.7 ml. of 0.1M acetate buffer, pH 4.45, was added to the hemolyzed red cells. The addition of the acetate buffer yielded a final pH of the solution of 5.5 to 5.6. The mixture was chilled in crushed ice for about fifteen minutes. At this time the red cell ghosts had flocculated to the bottom of the test tube. The mixture was centrifuged and the hemoglobin hemolysate removed steriley and saved. The red cell ghosts were then washed thrice with 0.01M acetate buffer of pH 5.6. After the third washing, the acetate buffer was carefully removed and the stroma mixed with two cc. of water. To the suspension 0.04 to 0.05 ml. of 0.01N sodium hydroxide was added to elevate the pH to 7.3 to 7.4. As the pH of the solution approaches neutrality, the suspension changes to an opalescent solution. This material was then placed in rubber-capped vials and frozen until used for skin testing procedures. Howe4 states that only one per cent of the hemoglobin is precipitated with the red cell stroma prepared in this way. All blood group agglu-

*In preparation and injection of these test materials, sterile technic was constantly used and all precautions exercised to avoid contamination.

† These fractions of plasma were prepared by Dr. C. B. Favour.
tinins and virus receptors remain on stroma prepared in this manner. No efforts were made to fractionate the stroma further. Careful observation of ionic strength of buffer solutions was necessary to obtain quantitative yields of stroma. It was estimated that the stroma dissolved in 2 ml. of water was equivalent approximately to a fifty per cent hematoctit of red cells.

4. Intradermal injection of hemoglobin: The hemoglobin solution that was removed from the red cell ghosts was transferred to sterile dialyzing tubing and dialyzed against cold distilled water for forty-eight hours. The solution was then lyophilized in sterile flasks. A brown powder was obtained which was stored in ampoules until used. The yield from one cc. of packed red cells was dissolved in two ml. of sterile saline solution for skin testing procedures.

5. Other procedures: In a few instances thrombin, fibrinogen, and histamine were used for intradermal testing.

Technic of skin tests. In all instances 0.1 cc. volumes were used for intradermal and subcutaneous testing. Tests were performed on the arms, forearms, and thighs. The skin was observed immediately, four to twelve hours, and then twenty-four hours after injection for edema and changes in color, and for erythema and induration. In some instances the area was observed for several days to note skin changes. All patients received packed washed red cells, stroma, and hemoglobin solutions. Case III also received packed washed red cells from a compatible donor. Likewise, all patients received stroma and hemoglobin solutions from normal donors. All patients and control subjects received physiological saline intradermally and, in some instances, phenolsulphthalein solution was administered to determine if patients were influenced by the colors of solutions in their subjective response.

Control studies: Ten women and twelve men received intradermal skin tests. Four of the women were patients with severe erythema nodosum.* The women were tested with red cell hematocrits of varying percentages, plasma, and serum. Two subjects received stroma and hemoglobin preparations.

All men were in good health except one with periarteritis nodosa. Three of these subjects received similar skin tests, on two occasions, and one subject received intradermal tests on three occasions. Four men received plasma fractions, stroma and hemoglobin preparations.

Results: Plasma.

None of the four patients nor any of the control subjects showed any abnormal response to plasma, serum or plasma fractions. Incubation of plasma, serum, or clotted blood for twenty-four hours did not produce any immediate or delayed intradermal response.

Red cells: The control adult volunteers showed no unusual intradermal reaction to various hematocrit concentrations of red cells. A residual amount of staining at the site of the intradermal injections of high concentration of red cells usually persisted for several weeks. This was not painful and had no surrounding erythematous response.

In contrast to the controls, our four patients showed varying degrees of response to the injection of red cell concentrations. In table 1 the skin reactions to the intradermal injection of various concentrations of red cells are tabulated.

Case I (L. A.) was studied at a period when she had spontaneous, painful ecchymotic lesions. This patient had no response to hematocrit concentrations of less than fifty per cent. However, a 60 and 80 per cent concentration of red cells produced a 2 x 3 cm. painful erythematous induration with central ecchymoses in twenty-four hours. Associated with these reactions the patient had

*These four patients were studied through the courtesy of Dr. C. B. Favour.
Table 1.—Skin area measurements after intradermal tests with various concentrations of red blood cells. The hematocrit preparations were prepared in general range of red cell concentration and were not identical in all studies. The columns labeled I and E differentiate the observed response as to induration and ecchymosis. The area of induration included erythematous reaction as well as indurated tissue by palpation.

<table>
<thead>
<tr>
<th>Hematocrit Concentration</th>
<th>I</th>
<th></th>
<th></th>
<th>II</th>
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<th>III</th>
<th></th>
<th></th>
<th>IV</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>L.A.</td>
<td></td>
<td></td>
<td>E.B.</td>
<td></td>
<td></td>
<td>R.G.</td>
<td></td>
<td></td>
<td>I.B.</td>
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<tr>
<td>10%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>50%</td>
<td>2 x 3</td>
<td>1.5 x 1.5</td>
<td></td>
<td></td>
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<td>60%</td>
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<td>80%</td>
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<td>2 x 2</td>
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<td>6 x 7</td>
<td>6 x 8</td>
<td>1 x 2*</td>
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* This reaction was not ovoid. The border was irregular and measurement is not exact.

I = Induration  E = Ecchymoses

large painful ecchymotic areas develop spontaneously on pressure areas (hips and arms) while she remained in bed (fig. 1). No further whole blood injections were given to this patient. The marked exacerbation of the painful ecchymotic areas precluded skin tests with red cells from a normal subject.

Case II (E. B.). This patient was studied five years after her last episode of painful ecchymoses. Within 12 hours after intradermal injection of red blood cells with an 80 per cent hematocrit, she had a painful erythematous indurated area around the site, measuring 2 x 2 cm. Within 24 hours, the 60 per cent red cell concentration was quite painful and had a one by two cm. area of induration. The area containing the eighty per cent red cell concentration was erythematous and showed ecchymoses. The patient described her response as similar to the earliest phases of her lesions, eight to ten years previously. Only limited observation could be done on this patient and no red cell studies from a normal donor were attempted.

Case III (R. G.) had a response of pain to the 80 per cent hematocrit concentration within four hours. At the end of sixteen hours, a large area of indurated painful erythema had developed and other sites of injection had similar reaction (figs. 2 and 3). As time passed, the injection of concentrated red cells became ecchymotic and continued to be indurated and painful. The photograph in figure 2 illustrates the areas of ecchymoses at forty-eight hours. The schematic drawing outlines the progression of these lesions more adequately (fig. 3). A skin biopsy was taken from the ecchymotic lesion produced by the injection of packed washed red cells with a hematocrit of 80 per cent. Microscopic study revealed no pathologic changes aside from extravasated red cells in the skin tissues. Figure 2 also demonstrates one other aspect of the response. Between the injections labeled 3 and 4 a fading skin test of an injection of a 50 per cent suspension of red cells, performed one week previously is present. The center of this lesion has cleared of the ecchymosis, but the border still remains tender, indurated, and ecchymotic. The induration and ecchymoses of all
lesions persisted for five to eight days and then began to disappear. An identical response was obtained using red cells in similar concentration from a compatible normal donor.

Case IV (I. B.). A response was noted in this patient with red cell concentrations above thirty per cent. The measurement of the lesions is outlined in table 1. The lesions associated with the intradermal injections were painful, especially the large indistinct indurated area associated with the 80 per cent red cell concentration. These studies resulted in spontaneous painful ecchymoses on the posterior thighs.

Stroma. Four normal volunteers received intradermal injections of stroma. Two volunteers received injections on three different occasions. None showed any response aside from a transient burning sensation when the material was injected. In contrast the four patients responded to stromal injections after a 24-hour period, as noted in table 2. All patients had similar responses to stroma suspensions prepared from normal donors.

Hemoglobin. No erythematous reaction or ecchymosis was observed in the
Fig. 3.—Case III. A diagram of measurements of skin lesions photographed in figure 2. The bracket numbers after the hematocrit percentage indicate the lesions as seen in figure 2. The solid black ovoid areas indicate indurated erythema while the cross-hatched areas represent ecchymotic lesions.

Table 2.—Response to intradermal injection of red cell stroma and hemoglobin. Hemoglobin solution caused no reaction. The column labeled Induration indicates the area of edema and erythema.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Induration (centimeters)</th>
<th>Ecchymoses (centimeters)</th>
<th>Pain</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. L.A.</td>
<td>5 x 5</td>
<td>1 x 1.5</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>II. E.B.</td>
<td>10 x 6</td>
<td>1 x 2</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>III. R.G.</td>
<td>5 x 8</td>
<td>3 x 4</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>IV. I.B.</td>
<td>5 x 7</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

volunteers or any of the four patients. Hemoglobin solutions from normal compatible donors also caused no response (table 2).

Miscellaneous. No unusual reactions followed intradermal administration of incubated serum or plasma-buffy coat preparations in the four patients. These studies were not done in volunteer subjects.

Discussion

The observations in this group of four female patients indicate a tissue sensitivity to extravasated red blood cells. All our patients had had an episode of
trauma associated with bruising which preceded the onset of the painful ecchymotic lesions. We believe that the term "erythrocyte autosensitization" can be used to describe what has occurred here. Previous clinical observations have suggested that generalized dermal sensitivity could develop from chronic eczematoid lesions. Whitfield has emphasized the concept of autosensitization for skin lesions. It is of interest that he observed two female patients who had hematomas and ecchymoses following trauma. Ten days later these patients developed a generalized erythematous skin eruption. Whitfield believed that these two women were examples of autosensitization from the extravasated blood in the hematomas. There are no comments that these patients had any pain with the erythematous eruption. This report is the only reference that we have found in the literature to suggest a dermal autosensitization to blood.

In acquired hemolytic anemia, in contrast to this tissue sensitivity, plasma factors have been demonstrated which agglutinate and lyse red cells in vitro. In fact, such plasma factors have been demonstrated for all of the formed blood elements. However, at the present time there is no proof that autosensitization entirely explains the pathologic physiology in acquired hemolytic anemia and in idiopathic thrombocytopenic purpura. Wagley and Castle were able to demonstrate, in the dog, the transient appearance of a positive Coombs test after the animals had been given injections of their own red cells. Liu and Evans have made similar observations in the rabbit. However, neither study demonstrated that the plasma factor was associated with the onset of anemia. Both publications lend further support to the concept that one may develop autosensitization if proper immunization has occurred. Past reports have documented specific tissue autosensitization to lens, kidney, skin, and muscle tissues.

The recurrent lesions observed in these patients may be confused with relapsing, febrile, nodular, non-suppurative panniculitis (Weber-Christian Disease). The onset of the lesions is associated with erythema and induration. In contrast to patients with panniculitis, none of the patients reported here have developed subcutaneous atrophy or nodules. Likewise, febrile reactions have been rare and only associated with a large extending ecchymotic area. As the ecchymosis disappeared, the skin became normal to palpation and appearance. Leukopenia was not observed.

Despite the frequent hematomas associated with trauma in hemophilia, painful ecchymoses due to a possible sensitivity reaction have not been reported. Likewise in ecchymoses seen in many types of purpura this response has not been described. Also, no case similar to the four here described has been seen in men. One may wonder if some tissue bleeding associated with the menstrual cycle may be a contributing factor to this type of tissue sensitivity in these four women.

While all our patients initially had painful ecchymoses from bruising, two patients had similar lesions develop elsewhere without known trauma. Also, these two patients had lesions develop elsewhere on the body when a painful ecchymosis followed bruising. To explain these distant lesions is difficult. Possibly they may be associated with physiologic tissue bleeding. If the tissue bleeding is accentuated by pressure (i.e., hips and thighs) an adequate concen-
tration of red cells might be present to initiate the reaction. Likewise these reactions may be associated with changes in general vascular permeability following the initial lesion during the periods of edema and further red cell extravasation. The presence of red cells in the normal Addis count and the pleural and pericardial bleeding associated with excessive anticoagulant therapy may be merely accentuation of tissue bleeding that is unrecognized in the normal person. The present studies would suggest that a certain concentration of red cells is necessary to initiate the tissue reaction. As may be observed in the skin test studies, no patient had an abnormal response until the hematocrit concentration of red cells was above 20 per cent. Dilution of whole blood with extravascular fluids may be adequate to lower the red cell concentration of physiologic capillary bleeding to prevent the onset of the hypersensitivity reaction.

In contrast to erythema nodosum or what has often been called Osler's disease, in which the patients develop first an area of redness and edema of the skin over the extremities, then evidence of red cell leakage and ecchymosis, the women here described have initial bleeding followed by redness, swelling and extreme tenderness out of all proportion to the bleeding phenomenon.

Three patients had episodes of abdominal pain associated with their painful bruises. In case I, the patient did not believe that her distress was localized in the left upper quadrant. However, she has never had a recurrence of abdominal pain following her splenectomy. Cases III and IV were observed repeatedly to have sharp, stabbing left upper quadrant pain when ecchymotic lesions existed. However, no pleural or abdominal friction rub was heard to suggest a splenitis and associated local peritonitis. In both patients roentgenograms of the chest failed to show pleural fluid, although on several occasions the left diaphragm was elevated because of limited inspiration. Usually this pain required opiates for the patient's comfort. Pathologic examination of the two spleens, cases I and II, removed surgically, were considered to show normal histology. Two patients, cases III and IV, had no abdominal distress until they were subjected to repeated intradermal skin testing. One may speculate that these procedures increased the sensitivity and the activity of the reticulo-endothelial system. However, splenitis was considered as a possible explanation for the abdominal pain despite the absence of splenomegaly by physical or roentgenographic examination.

Two of the patients had episodes of intracranial bleeding. It is not known if these neurologic lesions were associated with an abnormal response to extravascular red cells. Likewise, these two patients had gastrointestinal bleeding, and one patient had hematuria without explanation. These diffuse sources of bleeding may possibly be attributed to ecchymotic-like lesions. One cannot exclude a more diffuse vascular disease, present in these women, to account for many of the symptoms. Although the patients have been observed for many years, future study may reveal a more specific vasculitis associated with the red cell sensitivity.

No specific therapy is available for this form of purpura. Three of the four women have had a marked decrease of this abnormal response to bruising without explanation. Splenectomy was done in two patients. One patient had complete absence of the tissue sensitivity for a three-year period following
splenectomy only to have a recurrence which has persisted to a lesser degree until the present time. The other patient showed no improvement after surgery but gradually lost the abnormal tissue response during the next five years and is subjectively free of the painful bruising now. However, this latter patient still shows an abnormal response to intradermal skin tests with packed red cells.

Three patients received therapeutic courses of intradermal injections of whole blood, red cells or stroma. As the volume of the test material was increased, all of them had the onset of painful ecchymoses similar to those following trauma. Two patients had left upper quadrant pain which was accentuated after intradermal injections of red cells or stroma. This complication prevented further "desensitization" studies. As the patients have been observed over a period of months to years, there has been a gradual improvement in tissue sensitivity. Therefore, no type of intradermal desensitization procedure is recommended especially in consideration of the complications noted above. One patient had marked subjective improvement in control of pain and in the size of ecchymotic lesions following oral cortisone acetate. Such treatment may be used for comfort but one would hesitate to suggest prolonged steroid therapy in view of the complications from the induced hormonal imbalance.

The laboratory data indicate that these patients have an abnormal reaction to their own red cells when they have extravasated into extravascular tissues. A summary of the skin test responses to red cells and plasma factors is tabulated in table 3. The antigenicity of the red cell is present in the stromal lipoproteins and not in hemoglobin. It has been assumed that a fixed tissue antibody reacts with red cell stroma to produce edema, increased capillary permeability, and further extravasation of blood into the tissue. The lesion spreads by the further contact of the red cells at the periphery with sensitized tissue. Gradually the lesion ceases to spread. Possibly the accumulation of extravascular tissue fluid finally decreases the red cell concentration below the threshold necessary for reaction. Studies for hemolysis including antihuman globulin serum agglutination (direct and indirect Coombs test), mechanical fragility of red cells and studies for plasma agglutinins and hemolysins were non-contributory.

### Table 3.—A summary of the intradermal tests performed in the four patients studied. The evaluation of response is an arbitrary clinical classification.

<table>
<thead>
<tr>
<th>Intradermal tests</th>
<th>Patients I L. A</th>
<th>Patients II E. B</th>
<th>Patients III R. G</th>
<th>Patients IV L. B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Red blood cell hematocrit</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-60%</td>
<td>2+</td>
<td>1+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>80%</td>
<td>4+</td>
<td>3+</td>
<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td>2. Red blood cell stromal solution (50% concentration)</td>
<td>4+</td>
<td>3+</td>
<td>4+</td>
<td>2+</td>
</tr>
<tr>
<td>3. Hemoglobin solution (50% concentration)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Plasma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5. Plasma fractions—alpha, beta, gamma globulins; albumin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
One cannot emphasize too strongly the painful reactions of the intradermal tests in these patients. Only one patient was tested by the intradermal injection of packed red cells from a normal donor. This resulted in response exactly similar to that as seen with the patient’s own red cells. However, all patients had the same abnormal response to stroma preparations from compatible red cells of normal donors. The painful response to the skin tests with red cells and stroma has limited more complete study of these patients. A simple screening procedure by the intradermal injection of a patient’s whole blood or packed red cells may exclude this type of tissue sensitivity as a cause of purpura.

SUMMARY

Four patients with purpura who manifested an unusual response to bruising were studied. This response was characterized by the development of an area of painful ecchymosis at the site of trauma followed by progressive erythema and edema. This unusual tissue response was seen only in women. The various features of the cases suggested an autosensitization by the patients to their own blood.

Special studies utilizing skin testing procedures indicated an abnormal tissue response of sensitivity to red blood cells. The factor responsible was present in the red cell stroma and was not associated with the hemoglobin.

The clinical manifestations and possible therapy are discussed.

This syndrome may represent another example of autosensitization such as has been speculated for lupus erythematosus, some forms of acquired hemolytic anemia and of thrombocytopenic purpura, and for an increasing number of disease states.

SUMMARIO IN INTERLINGUA

Esseva studiate 4 patientes con purpura qui manifestava un inusual responsa a contusiones. Iste responsa esseva characterisate per le disveloppamento de un area de penose ecchymosis al sito del trauma sequite per progressive erythema e edema. Iste inusual tissue responsa histologic esseva observate exclusivemente in feminas. Varie caracteristicas del casos studiate supportava le conception que il se tractava de un autosensibilisation del patientes a lor proprie sanguine.

Studios special con tecnicas de essayage dermatic demonstrava un anormal sensibilitate histologic a erythrocytos. Le factor responsable pro iste responsa esseva presente in le stroma erythrocytic; illo non esseva associate con le hemoglobin.

Le manifestationes clinic e un possibile therapia es discutite.

Iste syndrome representa possibilemente un nove exemplo de autosensibilisation del typo considerate specularmente in lupus erythematosose, in alcun formas de acquirite anemia hemolytic e de purpura thrombocytopenic, e generalmente in un crescente numero de conditiones morbose.

REFERENCES

AUTOERYTHROCYTE SENSITIZATION


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Autoerythrocyte Sensitization A Form of Purpura Producing Painful Bruising Following Autosensitization to Red Blood Cells in Certain Women

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