The Demonstration of the “L.E.” Phenomenon in Patients with Penicillin Hypersensitivity

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RECENT EMPHASIS on the relationship between the hypersensitive state and collagen diseases led to a search for evidence of the “L. E.” phenomenon in patients with penicillin reactions. Our interest in this problem was first aroused by the demonstration of the “L. E.” factor in the plasma of an elderly white male with a severe penicillin reaction.

Penicillin hypersensitivity may be manifested as a serious systemic disease, producing a clinical picture similar to serum sickness. Harkavy reported a hyperergic type of vascular lesion, involving the connective vascular tissue of the lungs, heart, kidney, joints and skin in patients with penicillin reactions. Specifically he described “irreversible inflammatory alterations of the collagen tissue, capillaries and venules as well as necrotizing arteritis.” This author emphasized the similarity between these histologic changes and those seen in severe serum sickness. Rich showed a relationship of the hypersensitivity state to periarteritis nodosa, lupus erythematosus, serum sickness, and rheumatic fever. The occurrence of the “L. E.” phenomenon in patients with penicillin reactions as described below, also suggests a relationship of drug hypersensitivity to the collagen diseases.

METHODS

The procedure used to demonstrate the “L. E.” plasma factor was that of Hasenick and Bortz. In the 3 patients who showed the presence of the “L. E.” plasma factor, a concentrated heparinized marrow was examined for the “L. E.” cell, “pre L. E.” cell and rosettes.

The 6 patients selected for study had clinical evidence of penicillin reactions. In 3 patients there was a generalized, febrile illness, simulating serum sickness with severe skin lesions. Minimal urticarial lesions involving small areas of the body were the only evidence of drug hypersensitivity in the remaining three patients.

RESULTS

The 6 patients studied fell into two groups. In each of the 3 patients with severe penicillin reactions the plasma “L. E.” factor was demonstrated. Furthermore, in each case, “L. E.” cells were found in a study of the concentrated heparinized marrow. These patients are reported in detail below. The plasma of the remaining three patients, all of whom had mild urticarial reactions failed to reveal the presence of the “L. E.” factor.

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CASE REPORTS

Case I

T. H., a 63 year old white male was admitted to the Veterans Administration Hospital, Omaha, Neb., on March 10, 1952, because of arthralgia and a purpuric rash appearing after a course of 14 injections of penicillin. He had had pain in the shoulders, cervical region, elbows, hands and knees for approximately three years. In January 1951, he had been treated for an episode of "virus pneumonia" with an apparently uneventful recovery. In December 1951, he developed an upper respiratory infection associated with pain in the chest and coughing, which was treated by 14 daily injections of penicillin. Approximately one day after the last injection of penicillin, giant urticaria appeared extending over the face and lower extremities, and was followed during the next few days by multiple purpuric areas. Joint pains had been present intermittently since the onset of the rash.

On examination of the chest there was dullness and inspiratory rales over the right posterior chest. Arterial pressure was 140/96 and the heart was not enlarged. The spleen was thought to be felt just below the left costal margin, but the liver was not palpably enlarged. There were two small (1 by 1 cm.) nodules, one on the extensor surface of the left arm, and the other over the right achilles tendon. Mild fusiform swelling of the proximal interphalangeal joints of both hands was noted. There were irregularly shaped purpuric and ecchymotic lesions over both lower legs, and apparent remnants of purpuric lesions on the thighs.

The significant features of the hemogram were a leucocyte count of 9,200 with a normal differential analysis, and a platelet count of 146,000 per cu. mm. of blood. The total serum protein level was 8.1 Gm. per 100 cc., with albumin 3.5 and globulin 4.95 Gm. per 100 cc. There was 5 per cent bromsulfalein retention in 45 minutes, a thymol turbidity level of 12 McLageni units. The cephalin-cholesterol flocculation test was plus at the end of 48 hours. The prothrombin time was 100 per cent of normal.

The Kahn and VDRL tests for syphilis were negative. Repeated cultures for fungi in the sputum were negative. Urinary sediment included red blood cells, a number of red blood cell casts, occasional oval fat bodies, a few granular casts and a number of hyaline casts; albumin was not found in any specimens. Repeated roentgenograms of the chest showed diffuse scattered densities throughout both lung fields. Also a right hilar mass was seen, assumed to represent mediastinal lymphadenopathy. The bone marrow on March 18, 1952, using the particle preparation, showed no significant abnormality. On March 20, 1952, a concentrated, heparinized bone marrow specimen contained "L. E." cells. On April 2, 1952, a test for the "L. E." plasma factor was positive, showing typical "L. E." cells and rosettes. On April 30, 1952, the "L. E." plasma factor was again demonstrated. As before, many "L. E." cells were seen with an occasional rosette. A heparinized concentrated marrow specimen obtained on June 2, 1952, again revealed typical rosettes and the "pre L. E." cell. A liver biopsy was interpreted as "nonspecific degeneration and regeneration of liver tissue with no evidence of vascular lesions." A biopsy specimen of calf muscle revealed no abnormalities. A subcutaneous nodule removed from the extensor surface of the forearm was described as consistent with a diagnosis of a subcutaneous rheumatoid nodule.

During the first two weeks in the hospital the hemorrhagic skin eruption gradually faded and disappeared. The patient's arthralgia cleared, on the administration of salicylates, and, on discharge, he was apparently well.

Case II

J. M., a 57 year old white male entered the Psychiatric Ward on February 25, 1952, with a diagnosis of involutional melancholia. Penicillin ointment was administered to pyodermic areas on the neck daily from February 26 to March 26, 1952. During the last four days of this period 200,000 units of Crysticillin were given intramuscularly daily, as preparation for dental extractions. On March 26, a generalized erythematous rash was noted followed by diffuse desquamation, diagnosed by the dermatologist as a generalized exfoliative dermatitis.

Examination revealed the liver to be palpable 3 cm. below the costal margin and moder-
atly tender; the spleen was palpable just below the left costal margin. The skin lesions described above were present. There were no other significant physical abnormalities.

Blood counts revealed as the only abnormality an eosinophilia ranging from 6 to 11 per cent. No significant abnormalities were found in the urine. The Kahn and VDRL tests for syphilis were negative. The initial total serum protein determination revealed a value of 5.8 Gm. per cent, with albumin 3.5, and globulin 2.3 Gm. per cent. The results of subsequent serum protein determinations were within the same range. Tests of liver function revealed 3 per cent retention of bromsulfalein in 45 minutes, a thymol turbidity level of 0.6 McLagen units, and a negative result with the cephalin-cholesterol flocculation test at 48 hours. A roentgenogram of the chest showed no abnormalities. An electrocardiogram was within normal limits. On April 17, three weeks after the appearance of the skin eruption, a test for the plasma “L. E.” factor revealed characteristic “L. E.” cells (fig. 1). On the same date a bone marrow preparation using the particle technic contained a marked increase in the number of eosinophilic granulocytes. A concentrated, heparinized bone marrow preparation on the same date revealed a number of “L. E.” cells. One month later (May 20, 1952), a

test for the “L. E.” plasma factor again revealed a number of typical “L. E.” cells and “pre L. E.” cells (fig. 2), as well as a number of rosettes.

The subsequent course of the patient was uneventful. With symptomatic treatment the skin lesions progressively cleared, and after one month disappeared. On June 6, nine weeks after the appearance of the initial skin lesions and six weeks after the first test for the plasma “L. E.” factor was performed, a concentrated heparinized marrow specimen again contained an occasional “L. E.” cell, an occasional “pre L. E.” cell and a few rosettes, fewer in number than had been previously demonstrated.

Case III

A. B., a 53 year old white male, entered the hospital on May 21, 1952 because of skin lesions of one week's duration. These had appeared ten days after being given parenteral penicillin for a suppurative infection of the finger. The eruption started as a blotchy, reddened, elevated area over the upper and lower extremities, then extended over most of the body surface, and soon began to scale. Associated with this there was severe pruritus and pain in the joints of the feet. The patient stated that he had never taken penicillin prior to this occasion and that the only skin disease he had had in the past was an episode of scabies while in military service. The only history of hypersensitivity was the statement that he was sensitive to wool.

Physical examination revealed a generalized, weeping, erythematous, crusted and
scaling eruption which was more prominent over the lower extremities. In addition, there were lesions thought to resemble erythema multiforme. The liver and spleen were not palpably enlarged. There was generalized adenopathy but the remainder of the physical examination revealed no significant abnormalities.

The only abnormality of the hemogram was a leukocyte count of 12,900 with 4 per cent eosinophils. The Kahn and VDRL tests for syphilis were negative. The urine contained a few clumps of red blood cells, an occasional granular cast and an occasional oval fat body. The total serum protein level was 7.35 Gm. per cent, with an albumin level of 3.1 Gm. per cent and a globulin of 4.25 Gm. per cent. There was 4 per cent retention of bromsulfalein in 45 minutes, and a thymol turbidity level of 1.2 McIlagen units. A roentgenogram of the chest was within normal limits. A bone marrow particle preparation on June 2, 1952 contained a distinct increase in the number of eosinophilic granulocytes. A concentrated, heparinized marrow specimen on the same date showed an occasional typical "L. E." cell and rosette. A few "pre L. E." cells were also seen. On May 23, 1952, the test for the "L. E." plasma factor revealed only an occasional "L. E." cell.

The patient's course was quite uneventful. His skin lesions rapidly receded under treatment with local applications. A test for the plasma "L. E." factor performed on June 6, 1952 failed to reveal "L. E." cells, "pre L. E." cells or rosettes.

**COMMENT**

Among the 6 patients studied the "L. E." phenomenon was found in 3 with severe penicillin reactions and not found in 3 with mild reactions.

The significance of a positive "L. E." test in patients with penicillin reactions may have one of a number of implications: (1) that the test is nonspecific for systemic lupus erythematosus and may be found in unrelated conditions; (2) that penicillin reactions may produce pathologic and serologic changes related to systemic lupus erythematosus; (3) that the "L. E." phenomenon may be related to hypersensitivity without the histologic change of systemic lupus erythematosus; (4) that there is coincidental lupus erythematosus present.

The specificity of the presence of the "L. E." factor for systemic lupus erythematosus can be finally answered only with additional experience with the procedure. "L. E." cells have been found in 1 case of hemolytic anemia,12 pernicious anemia,13 dermatitis herpetiformis,13 leukemia,14 multiple myeloma,15 and miliary tuberculosis16 respectively. A pseudo "L. E." cell has been described in amyloidosis.17 No mention is made in these reports regarding confirmation of the findings by repeated bone marrow examinations for the presence of the "L. E." cells, or by reproducing the phenomenon using the plasma from these patients. Berman et al.18 have stated that they found "L. E." cells "in patients with disease unrelated to lupus erythematosus or in which the diagnosis of lupus erythematosus or related diseases could not be clearly established."

Haserick17 has reported the simulation of the lupus erythematosus phenomenon by contamination of the plasma sample with materials of fungal origin, implicating the Aspergillus group in particular. Furthermore, this author referred to a patient with lupus erythematosus reported by Soffer and his associates18 who was found to have a fungus infection of the lungs at autopsy. Recently Gausewitz, Jones and Worley19 reported the occurrence of one "L. E." cell in a patient with fatal generalized moniliasis. Although the significance of this group of observations requires further study, there has been an increasing amount of recorded data supporting the reliability and specificity of the "L. E." phenomenon for systemic lupus erythematosus.10, 12, 20-28

With demonstration of a high degree of specificity for the "L. E." phenomenon,
its occurrence in severe penicillin hypersensitivity suggests a relationship with systemic lupus erythematosus. Severe penicillin reactions may show many similarities to serum sickness including polyarthritis, pulmonary infiltrations, eosinophilia and purpuric skin lesions. Furthermore, the histologic changes shown by these patients have been shown to be similar to those seen in serum sickness. These have been shown to include inflammatory alterations of the collagen tissue, capillaries and venules as well as a necrotizing arterial lesion. Such observations are in keeping with those of Klinge and his associates, as well as of Rich, showing the interrelationship of the group of diseases called "the collagen diseases," and their association with the hypersensitivity state. The relationship between the hypersensitivity state induced by drugs and these "collagen diseases" has been particularly stressed by Rich.

Since lupus erythematosus is a "collagen disease" reportedly related to the hypersensitivity state and since penicillin reactions have been shown to be capable of producing hyperergic vascular and connective tissue changes, it seems possible that a penicillin reaction may produce lupus erythematosus. Indeed this possibility has been suggested by Gold in a thoughtful clinical analysis of the pathogenesis of this disease. In this connection, it is of interest that a patient recently reported by Dubois developed apparent systemic lupus erythematosus after contact with hair dye. An analysis of the sequence of events in this patient suggests to us an allergic response to the dye.

The third possibility cited, that the "L. E." phenomenon occurs in hypersensitivity states and is not necessarily related to histologic changes such as those seen in collagen diseases, cannot be evaluated from the available data.

The presence of the "L. E." phenomenon in these patients with severe penicillin reactions may represent coincident systemic lupus erythematosus. The clinical picture in T. H. is compatible with this diagnosis. While the occurrence of lupus erythematosus in the male has been said to be low, nevertheless, the data available at present are not sufficient to exclude the diagnosis of systemic lupus erythematosus in this patient. It is the opinion of the authors, however, that this is unlikely. In the other 2 patients no clinical supporting evidence for the diagnosis of lupus erythematosus could be obtained. A related question that must be considered is the unlikely possibility that the "L. E." factor was present in these patients before the administration of penicillin.

SUMMARY AND CONCLUSIONS

Of 6 patients with penicillin reactions, 3 whose reactions were severe were found to possess the "L. E." factor in the plasma and "L. E." cells in the bone marrow. The 3 who failed to show the "L. E." phenomenon had only minimal reactions to penicillin. Since the group studied was small, no conclusions regarding the incidence of the "L. E." phenomenon in penicillin reactions can be drawn. The findings are discussed in the light of the possibility that the phenomenon may be related to hypersensitivity reactions as well as to systemic lupus erythematosus.

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