

Scurvy and Hemarthrosis

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● Scurvy developed in a 56-year-old man with poor dietary intake and was associated with knee hemarthroses and synovial thickening. The synovial membrane showed interstitial hemorrhage and many large fibroblasts but little collagen and some disarray of vascular basement membrane. Hemarthroses and all knee symptoms completely resolved on a normal diet. To our knowledge, these are the first electron-microscopic studies of synovial membrane in human scurvy, and our findings support a defect in collagen synthesis as a factor in etiology.

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HEMARTHROSIS may be seen in trauma,¹ hematological diseases,²⁻⁴ neuropathic joints,¹ and a number of other conditions.⁵⁻⁷

Another cause of hemarthrosis, often neglected, is scurvy.^{8,9} The purpose of this report is to reemphasize the occurrence of this complication and to present both light- and electron-microscopic observations of synovial biopsy material.

Report of a Case

A 56-year-old male bartender gave a three-week history of mildly painful swelling of his right knee and lower leg. He denied any antecedent trauma or systemic symptoms such as fever, chills, myalgia, or pain in other joints. He had not been eating well and thought that he had lost about 4.5 kg over the past few months. He had a background of heavy smoking, alcohol abuse, and untreated hypertension. He had sustained two cerebrovascular accidents resulting in right hemiparesis and the inability to speak and move his tongue, and he had severe difficulty initiating deglutition. Until the onset of swelling in his leg, he had been able to walk with the aid of a cane.

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On admission, the patient was alert and moderately cachectic. His blood pressure was 110/60 mm Hg without orthostatic change; pulse rate was 80 beats per minute and regular, and he was afebrile. He had bilateral subconjunctival hemorrhages; paramolar mucosal hemorrhages at the second and third molars; and a smooth, poorly papillated, moist tongue. There were multiple petechiae present under most fingernails. The right knee was swollen with a ballotable patella. The suprapatellar pouch on the right was enlarged, but there was no crepitus or instability. The right leg was edematous. The Homan sign was absent bilaterally, and pulses were normal. The bases of old burn scars on the right leg were noticeably hemorrhagic. The left leg was normal except for a small effusion in the knee. Mild perifollicular hyperkeratosis was noted on the skin over the buttocks, thighs, and upper part of the arms. Pain sensation was normal.

Laboratory tests showed a hemoglobin level of 6.7 gm/100 ml and a hematocrit reading of 21%. The white blood cell count was 5,000/cu mm, with a normal differential cell count. The prothrombin time and partial thromboplastin time were also normal, and Coombs test was negative. The peripheral blood smear showed oval macrocytes, a few microcytes, and mild anisocytosis but no hypochromia. The polymorphonuclear leukocytes were hypersegmented, but no toxic granulation was seen. Platelets were slightly increased in number and the reticulocyte count was only 1%. Stool guaiac test for blood was negative. A bone-marrow aspirate showed megaloblastic changes and adequate iron

stores. Folate and vitamin B₁₂ levels were 2.3 ng/ml and 460 ng/ml, respectively, showing a substantial deficiency of folate but a normal range for vitamin B₁₂. Sick-cell preparation was negative and the glucose-6-phosphate-dehydrogenase level was normal. Hemoglobin electrophoresis showed type AA, and serum protein electrophoresis demonstrated a decrease in albumin level to 37.5% and an increase in α_2 - and γ -globulin levels to 13.2% and 30.4%, respectively (total protein level was 7.4 mg/100 ml). Levels of blood glucose, electrolytes, urea, creatinine, and total bilirubin were within normal limits. Results of urinalysis were normal. Chest roentgenogram and electrocardiogram were also normal.

Roentgenograms of the right knee showed no evidence of fracture, dislocation, or intrinsic bone disease, though there was noticeable soft-tissue swelling. Aspiration of the right knee joint yielded 35 ml of grossly bloody fluid, with a hemoglobin level of 3.9 gm/100 ml and a hematocrit reading of 9%. The white blood cell count was 1,200/cu mm with 60% polymorphonuclear leukocytes and 40% mononuclear cells. The total protein content was 6.5 gm/100 ml, and the glucose level was 71 mg/100 ml. (Peripheral blood protein and glucose levels were 7.6 gm/100 ml and 100 mg/100 ml, respectively.) No fat, crystals, bone spicules, or bone-marrow elements were seen. Gram stain and acid-fast bacillus stain of this fluid demonstrated no organisms, and bacterial cultures were negative. Twenty-five milliliters of grossly bloody fluid were also aspirated from the left knee, with essentially the same hematocrit reading, white blood cell count, and protein levels as in the right knee. Plasma assay for ascorbic acid, obtained two days after admission, yielded a value of 0.5

Fig 1.—Synovial membrane showing many large elongated fibroblasts and smaller erythrocytes scattered throughout interstitium (hematoxylin-eosin, $\times 360$).



mg/100 ml (normal, 0.4 to 1.5 mg/100 ml in our laboratory).

A synovial biopsy specimen of the right knee, obtained with a Parker-Pearson needle, showed massive fresh hemorrhage into the synovium (Fig 1) as well as some hemosiderin in the macrophages of the deep connective tissue, suggestive of older bleeding. No evidence of inflammatory cell infiltrate was seen, but there were increased numbers of unusually large fibroblasts. The synovial lining cells appeared normal, and Congo red stain for amyloid was negative. A portion of the synovium was immediately placed in half-strength Karnovsky fixative and processed as previously described⁷ for electron microscopy. The electron micrographs (Fig 2) showed many fibroblasts with prominent, dilated, rough endoplasmic reticulum, Golgi apparatus, and nucleoli. Occasional vacuoles containing ferritin granules and other dense, unidentified material were also noted. Mature collagen fibers were seen occasionally in the interstitium but were definitely decreased in number. Hemosiderin-laden macrophages were found, as were many extravasated erythrocytes and some erythrophagocytosis. Small-vessel endothelial cells were thick, with normal-appearing intercellular junctions, and were rich in organelles, including endoplasmic reticulum, Golgi apparatus, free ribosomes, dense bodies, and mitochondria. Vascular basement membrane was present but poorly defined, and perivascular collagen fibers were sparse (Fig 3). The pericytes had no identifiable alteration.

After four days on a balanced diet with ascorbic acid, folate, and other vitamin supplements, the patient's reticulocyte count and hematocrit reading began to climb, and he started to gain weight. His hemorrhagic manifestations, including the effusions in his knees, resolved and gradually disappeared in about two months. He was able to undergo physical therapy and began walking once again. When seen five months later, he had no knee effusions and was feeling well on an improved diet.

Comment

The following features support the diagnosis of ascorbic-acid deficiency in our patient. His diet was of poor enough quality for a sufficiently long period of time to allow at least one other vitamin deficiency (folate) to occur. The multiple hemorrhagic manifestations that rapidly cleared with vitamin replacement, and the follicular hyperkeratosis, were typical of ascorbic-acid deficiency. Nevertheless, the diagnosis of scurvy was not immediately recognized. A plasma ascorbic acid level was not obtained until after two days on a hospital diet, and therefore cannot be

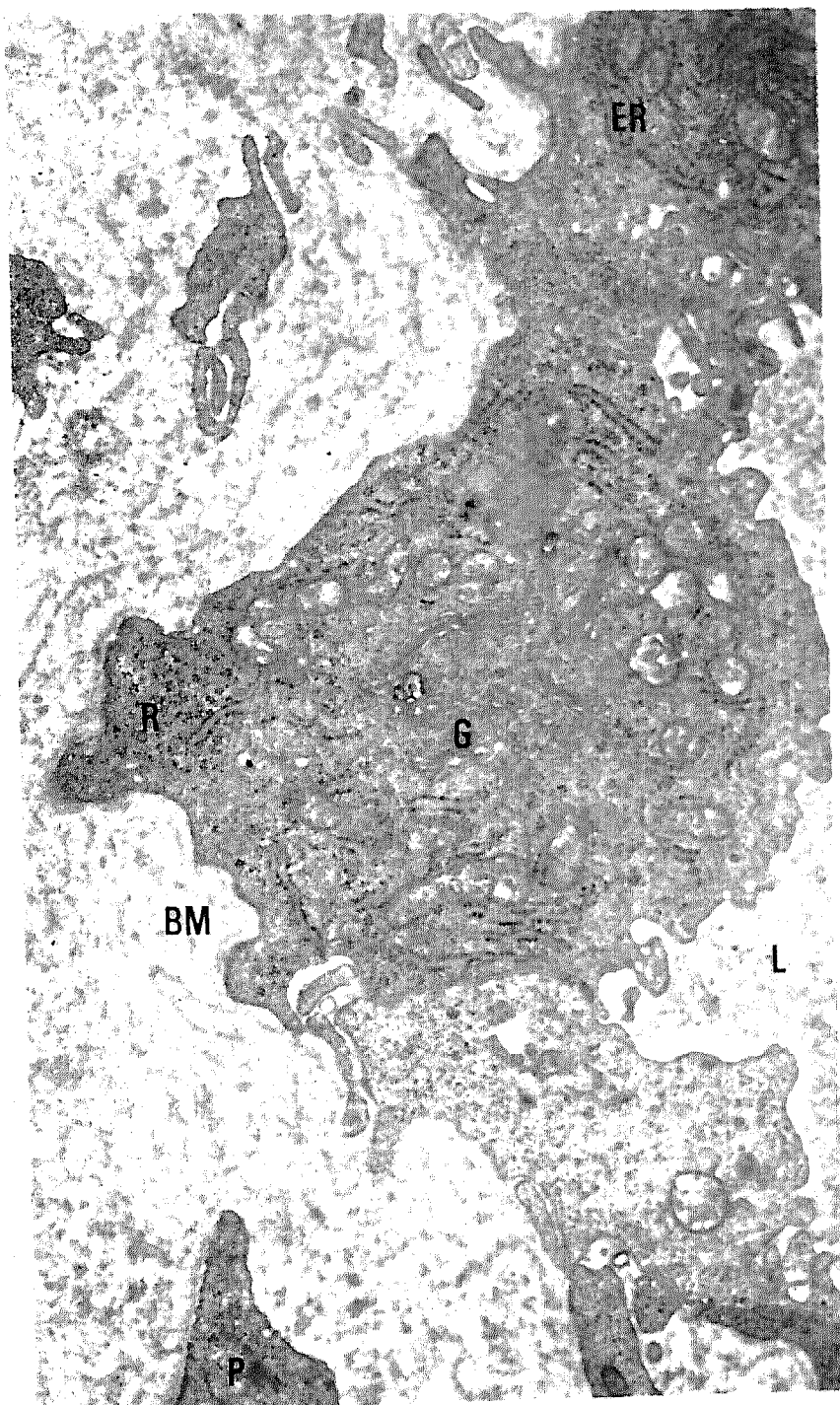


Fig 2.—Wall of synovial venule demonstrating identifiable but poorly defined vascular basement membrane (BM). No mature collagen is seen. L indicates lumen of venule; P, pericyte process; R, ribosomes; G, Golgi apparatus; and ER, rough endoplasmic reticulum ($\times 18,000$).

used as a reliable estimate of his total body stores, but his plasma level for ascorbic acid was found to be at the lowest limit of normal in our clinical laboratory.

The thick synovium was at least partly due to the interstitial hemorrhage demonstrated in the synovial tissue. The asymptomatic left knee

was completely normal except for an effusion that was grossly bloody. There is experimental evidence that trauma can aggravate the joint involvement of scurvy.⁸ This may account for the severe involvement in our patient's paretic leg, where the normal protective mechanisms were deficient.

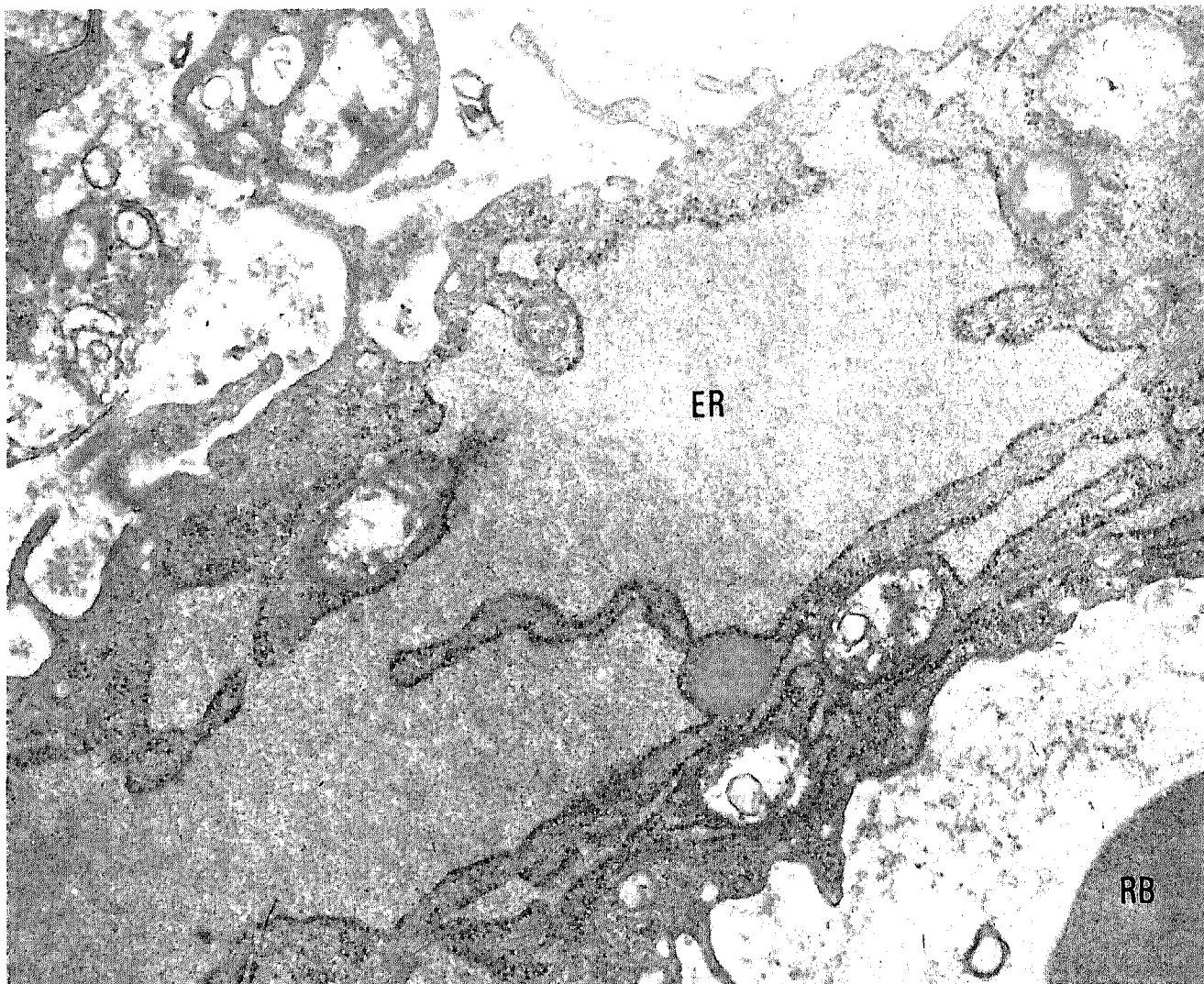


Fig 3.—Fibrocyte with massively dilated rough endoplasmic reticulum (ER) distended with finely granular material. No mature collagen is seen. RB indicates extravasated red blood cell ($\times 28,000$).

Ascorbic acid is a necessary cofactor for the hydroxylation of proline and lysine in the biosynthesis of collagen.¹⁰ In the absence of this vitamin, there is decreased synthesis of collagen and accumulation of collagen with abnormal structural characteristics.¹¹ The dilated endoplasmic reticulum noted in fibroblasts has been correlated with a deficiency in collagen synthesis and deposition.¹² Basement membrane synthesis is also impaired,¹³ and in experimental scurvy, vascular cells show ultrastructural changes similar to those noted in the fibroblasts.¹⁴ Loss of structural integrity of the synovial tissue and the trauma of normal activity in a joint might result in hemarthrosis and intrasynovial hemorrhage. Our biopsy material with its dramatic lack of collagen would seem to offer support for such a mechanism.

We offer this case not only to demonstrate the histological and ultrastructural characteristics of scurvy in the human synovium, but also to call attention to one cause of hemarthrosis that may be more common than appreciated.

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