Chapter 2

Joint Damage as a Result of Hemarthrosis

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The immediate symptoms or “short-term” effects of hemarthrosis are pain, swelling, warmth, and muscle spasm. The “long-term” effects of recurrent joint bleeding are more serious. Repeated episodes of intra-articular bleeding cause damage to the joint, leading to deformity and crippling [1, 2]. However, the delay between joint bleeding and the subsequent joint damage makes it difficult to establish the exact pathogenetic mechanism of blood-induced joint damage.

Recurrent hemarthroses, as occur in hemophilia, lead to specific changes in the synovium and cartilage, which finally result in total destruction of the joint. This process is called hemophilic arthropathy [3–8]. The pathogenetic mechanisms of hemophilic arthropathy are not precisely known.

Several joint disorders result in cartilage damage and changes in synovial tissue; these disorders can be degenerative, such as osteoarthritis, inflammation-mediated, such as rheumatoid arthritis, or blood-induced, such as hemophilic arthropathy. Several mediators are involved in these changes, for example, enzymes, cytokines, and oxygen metabolites. Current theories, which are based on experimental in vitro studies [2, 3] and clinical experience, suggest that the synovium becomes catabolically active because of excessive exposure to blood components, and as a result induces cartilage destruction. Synovial iron deposition, which can easily be detected by magnetic resonance imaging, is suggested to be indicative of the severity of hemophilic arthropathy. However, these theories are based on only a limited number of studies. In comparison to our knowledge about osteoarthritis and rheumatoid arthritis, little is known about the mechanisms of cartilage damage in hemophilic arthropathy. It is possible that the pathophysiology is multifactorial in origin and includes degenerative cartilage-mediated and inflammatory synovium-mediated components.

It is recognized that repeated extravasation of blood into the joint cavity is the factor responsible for synovial and cartilage changes [8, 9]. Synovial changes are thought to precede cartilage changes. Progressive accumulation of iron from red blood cells removed from the joint cavity by synovial macrophages over time, during successive intra-articular hemorrhages, has been postulated to be the trigger for synovial inflammation. This synovial inflammation would ultimately lead to joint damage that becomes evident years after the
first bleeding episode has occurred [10]. An important characteristic of synovial changes is the deposition of iron (hemosiderin) in the synovium. Experimental hemarthrosis induces synovial changes resembling those seen in patients with hemophilia. The hemosiderin deposits are thought to induce synoviocyte hypertrophy (resulting in villus growth), and neovascularization in the subsynovial layer (resulting in increased vascularity). Another suggested effect of the hemosiderin deposits is an infiltration of the synovial membrane with lymphocytes, although follicles of lymphocytes, which can be seen in the synovial membrane in rheumatoid arthritis, have not been observed. Compared with inflammatory arthropathies like rheumatoid arthritis there are only mild inflammatory changes. Synovial iron deposits as a result of recurrent intra-articular hemorrhages are also found in other joint disorders such as pigmented villonodular synovitis, hemangiomas of the synovial membrane, and hemosiderotic synovitis. These joint disorders all result in joint damage resembling hemophilic arthropathy, which suggests that synovial iron deposits indeed play an important role in the pathogenesis of blood-induced cartilage damage [11, 12]. Accumulation of iron, as a degradation product of hemoglobin, may be a direct stimulus for the proliferation of synoviocytes and attract inflammatory cells; the subsequent production of enzymes and cytokines could lead to the destruction of articular cartilage [13, 14].

In a study of patients with hemophilia who underwent elective orthopedic surgery of the knee, it was found that the synovial tissue in all patients showed areas with a hemosideritic appearance adjacent to areas of normal appearance [15]. This finding provided a model for an analysis of the effect of synovial iron deposits in synovial tissue. The macroscopic appearance corresponded closely to the histological iron deposits and, in addition, to the inflammatory and catabolic activity of the tissues. The results show that the iron deposits at localized sites in the synovium are associated with the production of pro-inflammatory cytokines and an ability to inhibit the formation of human cartilage matrix. This supports the hypothesis that iron plays a leading role in the induction of synovial changes and the consequent production of catabolic mediators that are harmful to articular cartilage. It is not clear whether hemosiderin is directly involved in the stimulation of cytokine production; it seems more likely that phagocytosis by synovial cells and blood macrophages released into the hemarthritic joint leads to the stimulation of cytokine production. However, the inflammatory changes in hemosideritic synovial tissue, as determined histologically, are mild compared with those in tissue with inflammatory joint disease such as rheumatoid arthritis [15, 16]. The potential for damage by hemosideritic synovial tissue underlines the importance of early diagnosis and treatment of chronic synovitis in hemophiliac patients.

In addition to synovial triggering, it has been suggested that intra-articular blood has a direct harmful effect on cartilage before, and independently of, the synovial changes, and that joint damage may occur before the synovial inflammation becomes evident; primarily there may be damage of articular cartilage with synovitis as a consequence. These studies demonstrate that the initial