Henry Ford Hosp Med Journal
Vol 27, No 1, 1979

Rheumatoid Arthritis

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Evidence that a particular disease existed in antiquity can be obtained from a variety of sources. For example, the art work produced by a civilization may provide examples of the pathologic process if a type of physical deformity is evident. Studying the exhumed remains of the members of the population may produce a more definite type of histologic documentation if the disease state has demonstrated specific tissue changes. Finally, in surveying the literature written during a defined period of time, one may find a clinical description of the disease recorded as a series of symptoms and signs.

History

In the case of rheumatoid arthritis, there is an absence of the characteristic joint changes of this disease in subjects depicted in paintings or represented in sculptures before 1800. In addition, paleopathologic findings from early civilizations have not produced convincing evidence that rheumatoid arthritis existed as a distinct disease.

A possible case of rheumatoid arthritis was reported from the 5th Dynasty of Egypt (around 2400 B.C.). The mummified hands of a fifty to sixty-year-old man were noted to be deformed by joint swelling, ulnar deviation of the fingers, hyperextension at the metacarpophalangeal joints, and flexion at the interphalangeal joints. The "clawing" presented in this specimen, however, was not entirely typical of rheumatoid arthritis. A single case of the disease has also been described in American Indian skeletal material.[1] During the excavation of 250 burials it was noted that one male member, approximately seventy-five years old, was buried with his knees in a flexed position rather than in the customary extended position. Almost all his joints were affected by slight lipping. It was suggested that the leg flexure may have been the result of rheumatoid arthritis affecting the soft tissues of the knee joints.

Medical literature provides definitive evidence of the existence of rheumatoid arthritis in earlier centuries. The earliest clinical description was given in 1676 by Thomas Sydenham. He described a type of arthritis that was dominated by a chronic course with superimposed episodic flares, which resulted in a hyperextension deformity of the proximal interphalangeal joints of the hand.

The first recognition of rheumatoid arthritis as a separate disease is found in the thesis published in 1800 by a French medical student named Augustin-Jacob Landré-Beauvais. He stressed the following points: 1) this form of arthritis selectively affected women; 2) it was a disease of the common person; 3) several joints were involved in the first attack; 4) pain was less than that associated with gout but the attacks lasted longer; and 5) joint motion remained difficult after the symptoms had subsided, with the affected joints being frequently deformed, swollen, and exhibiting a degree of ankylosis. The name rheumatoid arthritis was introduced in 1859 by Sir Alfred Baring Garrod, a physician to the West London Hospital.[2] These overall observations seem to suggest that rheumatoid arthritis is of fairly recent origin.

According to recent statistics (1978), 31.6 million Americans out of a total population of 211 million persons have some form of arthritis. In this arthritic group, 6.5 million persons or 20.5% are afflicted wtih rheumatoid arthritis.

Clinical Symptoms

In general terms, it is recognized as a systemic, chronic disease characterized by episodes of acute inflammation which are primarily manifested in the joints. It affects women more frequently than men, and the adult form usually appears between 30 and 45 years of age. Prominent symptoms are prolonged morning stiffness, polyarthralgia, joint swelling, muscle weakness, fatigue, weight loss, and disability. The most characteristic joint changes in rheumatoid arthritis are found in the small joints of the hands, the wrists, and the elbows. Less frequently, the hips, knees, feet, cervical spine, and temporomandibular joints are involved. The disease process usually affects the joints in a symmetrical pattern.

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Etiology

Through the years, a variety of agents have been proposed as the cause for this disease. Infectious organisms such as bacteria, mycoplasma, and an unidentified virus have been continually mentioned. In addition, certain predisposing conditions such as a genetic predisposition, changes in the endocrine balance like those that accompany emotional stress, and an altered immune response have also been implicated. Nevertheless, at the present time, the etiologic factor or factors responsible for rheumatoid arthritis are unknown.

The joints are the major site of action in rheumatoid arthritis, and most investigators accept that the initial insult, whatever its etiology, involves interaction with the synovial membrane. Secondary pathologic changes then take place in the synovial fluid, cartilage, bone and tendons.

Pathology

In order to delineate the pathologic alterations associated with rheumatoid inflammation, it is necessary to understand the structure and function of the normal synovial membrane. This membrane is derived from primitive mesenchyme and has a relatively simple pattern of construction. A single layer of synovial lining cells, or synoviocytes, is in contact with the joint space. Individual synoviocytes either lie close to each other or are separated by wider areas of intercellular matrix (Figure 1). Immediately beneath the synoviocytes is loose connective tissue which is composed of a meshwork of thin collagen fibers, elastic fibers, and reticulin fibers. Scattered throughout this supportive connective tissue base are fibrocytes, histiocytes, and a few mast cells. Many blood vessels are found as a major component of this subsynoviocytic tissue.[3]

Morphologically, synoviocytes have been divided into two types depending upon whether or not their cytoplasm contains abundant rough endoplasmic reticulum or numerous lysosomes. These cells have several functions that are reflected by their intracytoplasmic organization. A phagocytic function is expressed by their capacity to engulf particulate material such as preformed antigen-antibody complexes. In addition, synoviocytes have the capacity for pinocytosis by which fluid containing smaller molecular

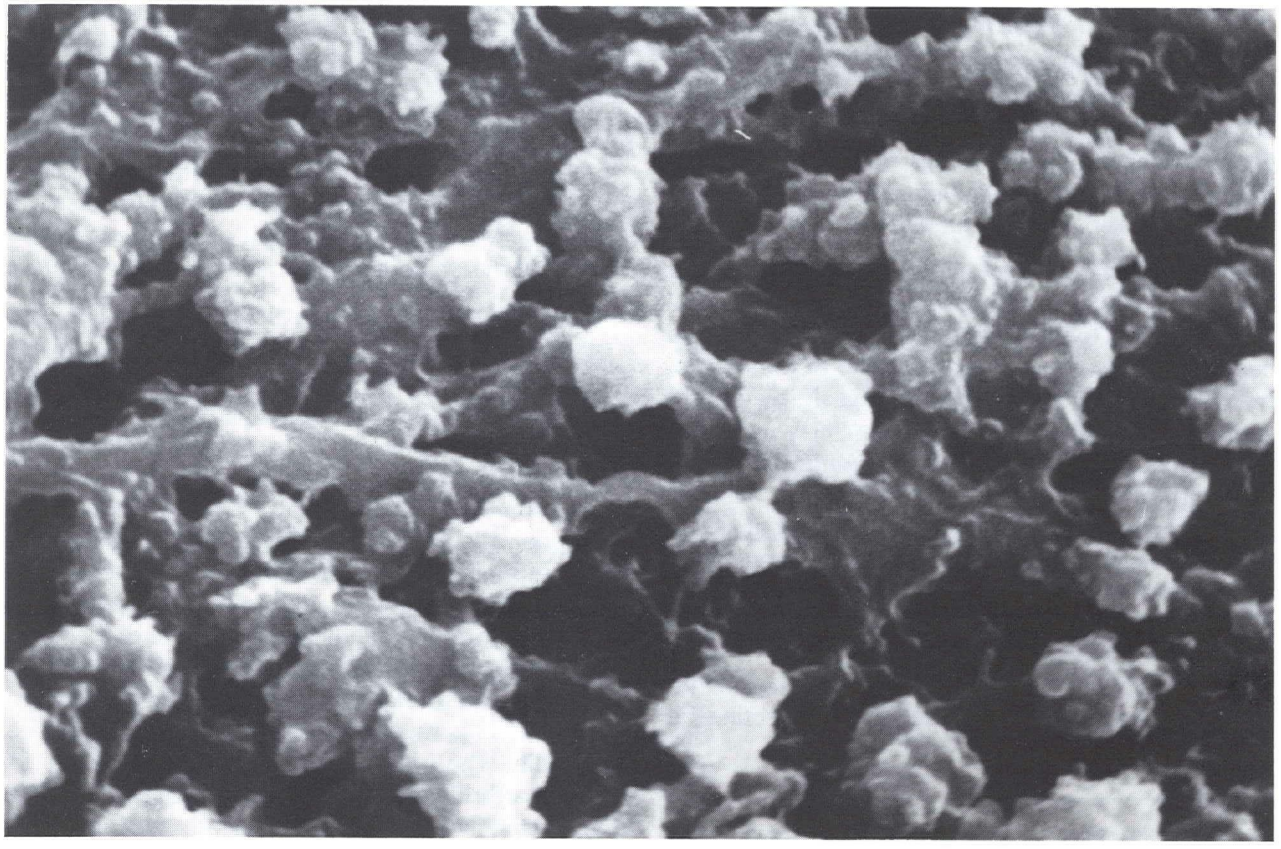

Fig. 1
The surface organization of the normal synovial membrane as viewed with the scanning electron microscope displays a single layer of synoviocytes separated by wide expanses of extracellular matrix (X5400).

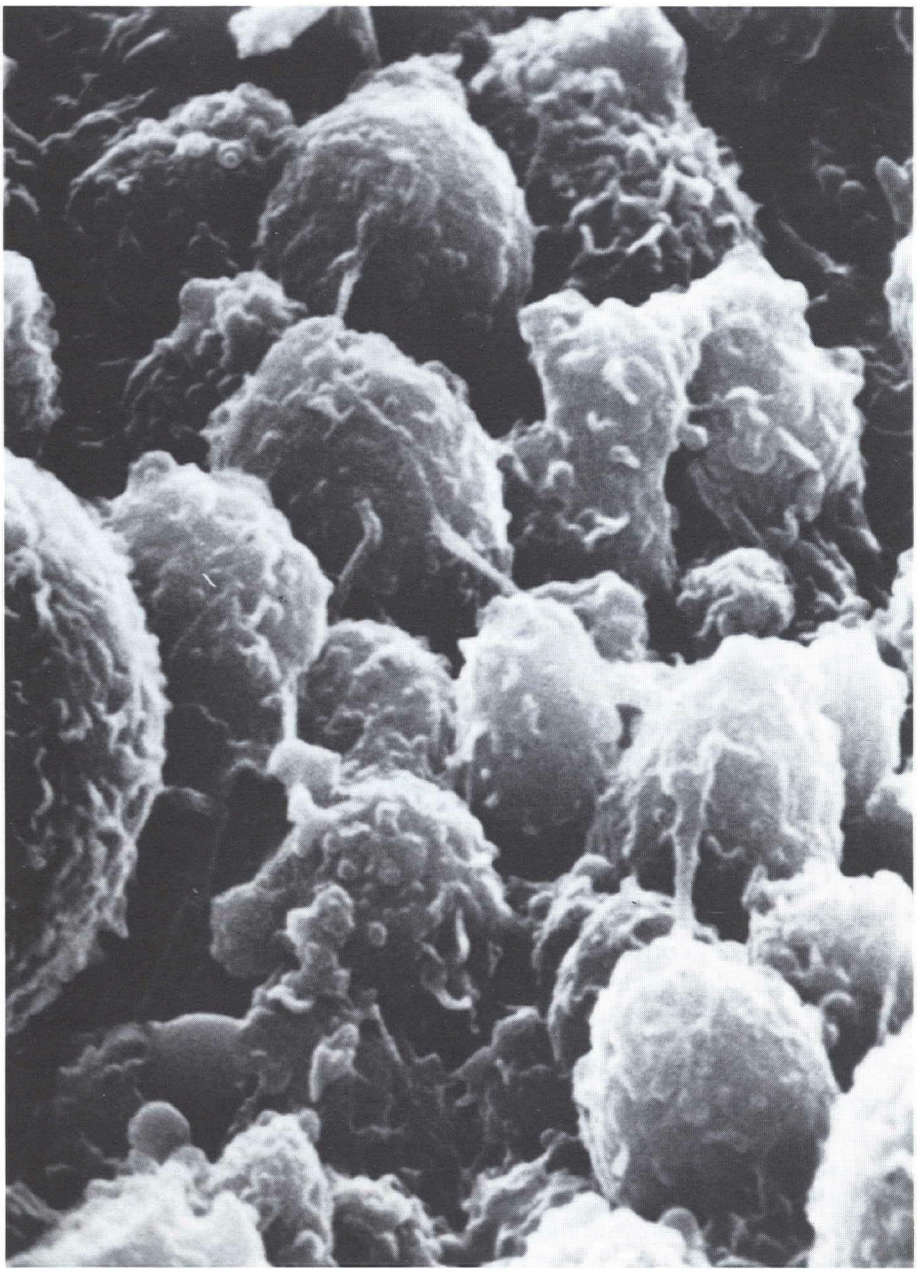

Fig. 2

During rheumatoid inflammation, the synoviocytes increase in number and are organized into several layers so that the thickness of the synovial membrane is greater than normal. In addition, single synoviocytes increase in size so that they lie close together and the extracellular matrix is minimal (X5800).

weight substances is internalized within cytoplasmic vesicles. Synoviocytes are also responsible for the synthesis of substances such as hyaluronate, which forms a part of the synovial fluid.[4]

The pathologic changes associated with rheumatoid arthritis are progressive and highlight its self-perpetuating quality unless the disease process is halted either by spontaneous remission or by appropriate anti-inflammatory drugs.

The inflammatory dynamics within an affected joint probably begin when the synovial membrane is insulted by an unknown etiologic agent(s). Acute inflammation ensues as a response to the tissue injury. In the connective tissue portion of the membrane, the endothelium of the blood vessels is altered so that gaps form between adjacent endothelial cells and plasma leaks into the extracellular space. Almost simultaneously, the pattern of blood flow changes so that the rate slows and the distribution of the peripheral blood elements in the lumen of the vessel is different from that seen during normal axial flow. Polymorphonuclear leucocytes emigrate from the altered blood vessels and accumulate extracellularly. Numerous erythrocytes appear to plug the lumen of the damaged blood vessel. The subsynovial tissue becomes edematous and infiltrated with exudative leucocytes, primarily neutrophils at this stage.

As a result of continuing inflammation, the inflammatory process becomes chronic so that the cellular components within the connective tissue base change. Lymphocytes become numerous and sometimes seem to organize into a collection that is reminiscent of a germinal center. Plasma cells and a few macrophages are also present.

Recent work has focused on the role of the lymphocytes within the rheumatoid synovium. From these studies has evolved the concept that rheumatoid arthritis has an autoimmune component. Briefly stated, the mechanism of this autoimmunity develops as follows. The patient's IgG is altered perhaps by an encounter with the unknown etiologic agent so that it is no longer recognized as self and becomes antigenic to the host. In response to this "foreign antigen," the plasma cells within the synovial membrane produce an antibody, or so-called rheumatoid factor. Interaction of the altered autologous IgG and rheumatoid factor then produces an antigen-antibody complex which utilizes complement and serves to reinitiate acute inflammation. The responding neutrophils phagocytize the particulate immune complex and release potent hydrolytic enzymes both within the synovial membrane and into the synovial fluid.[5] Fibrin may also be found within the synovial fluid[6] and on the exterior of the rheumatoid synovium. It also has the potential of selectively attracting neutrophils and recycling the acute phase of inflammation.[7]

As subsynovial changes occur, the synoviocytes also undergo structural alterations. Individual synoviocytes exhibit hypertrophy and increase in size at the same time as they also undergo hyperplasia and increase in number (Figure 2). The type of synoviocyte containing lysosomes predominates. In accordance with these cellular changes, the synovial membrane becomes thicker as the layers of synoviocytes increase in depth. The subsynovial tissue is edematous.

The swollen, edematous, inflammatory rheumatoid synovium is classified as a form of granulation tissue and referred to as pannus. As the pannus formation enlarges, it begins to encroach upon and partially cover the articulating cartilage. Certain biochemical events such as the release of lysosomal hydrolytic enzymes, collagenase and elastase from cells occur so that the underlying cartilage begins to degrade. Surface chondrocytes degenerate, collagen organization is disrupted, and the proteoglycan molecules are destroyed.[4] Eventually, as the erosive process continues, the subchondrial bone is exposed and bone cysts may form.

However, the earliest measurable bony change found in a joint affected by rheumatoid arthritis is a generalized demineralization. A more specific type of erosion follows later, and different cell types appear to play their respective roles in this process. One erosive pattern is characterized by the presence of numerous multinucleated osteoclasts. Another area of apparent bone erosion may be occupied exclusively by mononuclear cells. A third form of erosion appears to be produced by osteocytes which either enlarge the lacunar space which they occupied or are capable of demineralizing a region of bone in their immediate vicinity.[8]

As the disease progresses, inflammation of the subchondral bone produces further destruction of the bony cortex and irregular cyst-like areas of destruction in the cancellous tissue are formed. Subluxation and distortion of the joint often occur due to muscle contractures, and malalignments are quite characteristic (Figure 3).

When the rheumatoid inflammatory process subsides, organization of the pannus occurs and fibrous tissue proliferates. As part of the reparative process, fibrous adhesions join opposing epiphyses to produce fibrous ankylosis, which often proceeds to bony ankylosis by calcification and then to ossification. The bones are usually ankylosed or fixed in a flexed position, and the distorted joint is immobile and functionless.

Another manifestation of the rheumatoid inflammatory process is the rheumatoid nodule. Although it has been called the hallmark of seropositive rheumatoid arthritis, it occurs in only 25 to 30% of patients with rheumatoid arthritis. It is a subcutaneous nodule that tends to occur at pressure points on the body such as the elbows, but it may also be found

Fig. 3
The end result of chronic rheumatoid arthritis is frequently malaligned, ankylosed joints, as depicted by this functionless hand.

within certain internal organs such as the lungs. The rheumatoid nodule appears to form around a small blood vessel and has a distinct microscopic appearance. Three distinct zones of pathologic change are noted: 1) an area of central necrosis consisting of debris which includes cellular remnants, fibrin-like filaments, reticulum, and collagen fibers, 2) palisading fibroblasts, and 3) an outer zone of chronic inflammatory cells.[9]

Rheumatoid arthritis lacks any single, specific diagnostic x-ray finding. General features include evidence of osteoporosis, uniform diminution of the joint space, marginal erosions, malalignments and subluxations.

Summary

Rheumatoid arthritis is a systemic, chronic polyarticular disease in which the joints are affected symmetrically. Its etiology is unknown. The destructive joint changes are initiated by injury to the synovial membrane followed by a self-perpetuating inflammation with an autoimmune component. Cartilage and bone are eroded so that joint integrity is destroyed, and ankylosis, malalignment and subluxation result.

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