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## Rheumatoid arthritis : it's past and present effects

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Rheumatoid Arthritis:  
Its Past and Present Aspects.

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Senior Thesis

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## **Introduction**

## INTRODUCTION

Rheumatoid arthritis is at the present time one of the great diseases of medicine. With tuberculosis and syphilis it constitutes the great triad of chronic granulomatous infections prevalent in temperate climate. This is significant in the fact of explaining the rapidly growing interest in rheumatoid arthritis in particular. Increasing interest is also manifest because rheumatoid arthritis is one of the few remaining unsolved problems in the field of infectious diseases. In other diseases, many of which we know little of, we at least know their causes. The problem of etiology is still being debated and much work remains to be done before the problem can be settled. Other than etiology, we must also learn more about the influence of heredity, climate, individual constitution, malnutrition, and avitaminosis. Before treatment can be successfully carried out the foregoing factors must be better understood. Surveying present day interest as is manifested in the literature, one is greatly impressed and led to believe that if rheumatoid arthritis continues to interest workers as it does at the present time, there will

undoubtedly be a solution before many years to come.  
At the present time, it continues to be a challenge  
to every medical practitioner.

**Social and Economic Importance.**

## SOCIAL and ECONOMIC IMPORTANCE

Rheumatic disease represents one of the world's greatest social and economic problems. Of all patients admitted in 1933 to accredited hospitals in the United States, 97,984 patients (1.39 per cent) were admitted because of "arthritis or rheumatic diseases" (1). A recent Public Health Survey calculated the incidence of "chronic arthritis and rheumatic diseases" as 22.18 per 1000 persons, or 2.2 per cent of the population of which more than 1 per cent had "disabling" rheumatism and 0.85 per cent were "bedridden". Based on these figures, Kling calculated that about 2,700,000 of the 120,000,000 population in the United States are affected with chronic rheumatic diseases, of whom 1,230,000 are "disabled" and 1,020,000 have been bedridden at some time or other. Kling further believes this to be a low estimate. Fishbein (2) remarks, "Arthritis puts more people out of work than does the depression". Chronic rheumatic disease is not only an affliction, but a menace. Perplexed, patients with the disease stand face to face with what seems to them an impending evil whose tentacles spread out to affect their physical and material well being, and often their social



status, their economic resources and potentialities  
(3).

A Disease of Antiquity.

### A DISEASE of ANTIQUITY

Chronic arthritis is probably the most ancient of known diseases. Through the ages it has left its mark upon the skeletons of animal and man. Almost since life has existed in such form as to leave recognizable fossils, chronic arthritis has existed also. The period involved has been estimated by Moody (4) to be quite beyond our comprehension of time, perhaps six hundred million years. The changes found in some of the vertebrae of these remains, closely resemble the changes found in the spine of human beings at the necropsy table of a modern hospital. Pemberton (5) believes the pathology has been the same for about a hundred million years. A large mosasaurus (platecarpus) skeleton in the Museum of the University of Kansas shows articular changes characteristic of chronic arthritis in the foot bones, especially the first metatarsal and phalanges.

Bony change is seen in the various dinosaurs of the Comanchean period (110,000,000 years); the primitive ungulates of the Eocene (15,000,000 years); the Egyptian crocodile of the Miocene (15,000,000 years); the camel of the Pliocene (1,800,000 years); the cave bear and sabre-tooth cat of Pleistocene (500,000 years).

The "Ape Man" of the Pliocene age (1,800,000 years) suffered from "spondylitis deformans". The "Java Man" of the Pleistocene age (500,000 years) showed bony change of the femur, the earliest human pathological lesion. The neolithic man (75,000 years); the pre-dynastic Nubians and ancient Egyptians (8,000 years); and the pre-Columbian Indians of America all show typical lesions of chronic arthritis. The "Lansing Man" (500,000 years) had typical arthritic changes.

The disease was never found before the epiphyses had united. Sir Marc Armand Ruffer (6) in a study of ancient Egyptian mummies and skeletons describes examples of both atrophic and hypertrophic forms of arthritis. The skeletons covered a period of over three thousand years. Ruffer believes the disease to be different manifestations of one basic diathesis. He points out that the pathological anatomy of atrophic arthritis has not varied for over eight thousand years. The disease is older than history, common to animals and man, and distributed over the whole face of the densely populated portion of the earth.

**A Changing Conception of  
Joint Disease**

## A CHANGING CONCEPTION of JOINT DISEASE

The clinical picture of rheumatoid arthritis has persistently appeared in the writings of medical men since ancient time; but they knew little about the differentiation of joint disease. Hippocrates (7) thought, "the bile mingled with the blood in the veins and articulation, causing a swelling of the joints with the production of acute pain". Previous to the Sixteenth Century, the term arthritis referred to rheumatism, gout, and all other inflammations of the joints, ligaments, and muscles. From the Sixteenth Century on, the term rheumatism again came into use being formerly used by the ancients to denote a watery discharge from the mucous membranes. In 1610, William de Baillon (7a) published a thesis in which he distinguished between rheumatism and gout. In 1660 Sydenham (8) calls attention to the difference between gout and rheumatism and when the latter went from joint to joint with no fever but just swelling and pain, he preferred to call it arthritis.

From the time of Sydenham until 1800, there was no attempt by medical men to differentiate between various manifestations of joint disease. Garrod (9)

calls attention to the Thesis of Landré Beauvais in Paris, in 1800, in which the distinctive character of rheumatoid arthritis is distinguished from that of true gout, and arthritis deformans was claimed to be a distinct morbid entity. In 1804, Heberden (10) began to distinguish rheumatoid arthritis from true rheumatism and was the first to call attention to the nodules of the terminal phalanges. Although at this time, "rheumatoid arthritis" comprised both the atrophic and hypertrophic forms; Heberden's Nodes were the beginning of a system of differentiation between the rheumatoid and osteoarthritic types. Haygarth (11) in 1805 speaks of a troublesome disease in the joints, manifestly different from gout and from both acute and chronic rheumatism. Haygarth's clinical and pathological picture of the disease conforms to both the atrophic and hypertrophic forms of arthritis.

The pathological change in the joints was first noted by Scudamore (12) in 1819 for he said the process began by inflammation of the synovial membrane, then the involvement of the capsular ligament and cartilage. Although he noticed later bony change also to occur; he was first to define the initial lesion. In the mid Nineteenth Century we find such prominent writers

as Brodie (13), Jackson (14), and Monell (15) describing typical cases of atrophic and hypertrophic arthritides, but as yet unable to distinguish between the two diseases, Jackson remarking of the most common occurrence of the articulo-fibrous (rheumatoid) type. They all noticed the disease had characteristics of a low grade inflammation and had extensive factors of differential diagnosis to distinguish it from the acute rheumatic fever, and from gout. Fuller (16) at this time noticed the idiopathic nature of the occurrence of the hypertrophic form and the fact that the atrophic arthritis occurred in those already with visceral manifestations. Barwell (17) in England was calling attention to the thickened joint membranes present in the disease.

In 1876 Paget (18) believed chronic arthritis to be a disease of the bones. He noticed the atrophic form started by chronic inflammation in the membranes to be followed by bone absorption and atrophy and also noticed in some cases the hyperostoses of bone. Barwell (19) in 1881 agrees to Paget's interpretation but in his discourse also describes Volkmann's pathological findings in Germany and relates that he cannot agree with Volkmann, that the malady commences wholly



in the synovial membrane.

Smith (20), in 1881, speaks of the rheumatoid arthritis as "synovio-arthritis", because he states it has an organized, pulpy granulation tissue endowed with the peculiar tendency to infect, or absorb, or assimilate every form of fibrous tissue which it meets; it also eats its way through the articular cartilage and taps the marrow cavity. In contrast to this is the "medullo-arthritis" (as it starts in medullary substance of the bone). He proposes to call this "osteo-arthritis".

It is interesting to relate how carefully and accurately Charcot (21) in France in 1881 observed this ancient common disease. In the atrophic forms, he noticed the rapid onset, the affection of younger persons, little or no tendency to the formation of new bone, and the swelling and eventual ankylosis. He describes the hypertrophic type as being more gradual in its onset and course, as affecting older persons (40 - 60 years) and noticed there was periarticular bony outgrowths. Garrod (22) in 1890 crystallized the current thought of the time by making the nomenclature definite. He christened the atrophic type "rheumatoid arthritis" and the hypertrophic type

"osteo-arthritis". This useful classification has now been adopted in the United States.

In 1897, Still (23) described a joint affection in children with the clinical symptoms and morbid anatomy of rheumatoid arthritis in the adult. This has henceforth been known as Still's Disease.

Sixty-five autopsy cases of chronic arthritis were studied grossly and microscopically by Nichols and Richardson (24), in 1909. In their classical description, they give the exacting pathology of the atrophic or proliferative arthritis as contrasted with the hypertrophic or degenerative arthritis. This work was accepted world wide as the first real pathological description of the two diseases and minor detail was also added by Fisher (27) in England and by Allison and Ghormely (28) in America. The essential pathology described by these writers are contained within this discourse. The pathology has emphasized the essential quality of the disease.

## **The Concept of Pathology.**

## THE CONCEPT of PATHOLOGY

Knowledge of the pathologic changes in rheumatoid arthritis is not as complete as might be desired because of the rarity of a fatal termination during the acute and active stages of the disease. The majority of autopsy cases present but the scarred remains of a once active inflammatory process. The nature of tissue changes occurring elsewhere in the body, with the exception of the subcutaneous nodules, remains more obscure.

Nichols and Richardson (24) in their classical description of "proliferative" arthritis classify the pathological types as follows: serous, ulcerative, ankylosing, formative and fungus. Strangeways (25) classifies the rheumatoid group into the following six types: capsular, dry, adhesive, rarifying, villous and infective. The classification of Nichols and Richardson has been most preferable because it is based upon the most striking gross pathological feature in any particular rheumatoid joint. It should be noted that different joints in the same patient may belong to different types, or any individual joint may present mixed pathological features; for instance,

ulcerative changes in the articular surfaces may co-exist with villous or fungus changes in the synovial membrane. Fisher (26) points out, however, that in all these types the actual microscopic features in the individual joint elements present a general similarity and he proposes to discuss in turn the changes:

(1) in the synovial membrane and capsule,

(2) in the cartilage and bones.

In the following description of pathological structure as given by Fisher (26), the microscopic features will be incorporated in the general descriptions.

#### 1. Synovial and capsular changes

Since the synovial membrane is merely a specialized portion of the capsule, they may well be described together. There is often a striking increase in the number and size of the synovial villi. On opening such a joint, the long villous processes, some of which are very delicate, all of which are inflamed often protrude through the capsular opening. Necrosis and hemorrhage into some fringes may be seen. When the affected membrane is submerged in water, the extreme villosity may be noted. The number, size and distribution of the villi differ from that seen in the osteoarthritic variety in which the enlarged villi are less

numerous or prominent and usually occur in the immediate vicinity of the articular margins. The microscopical appearances in the synovial membrane is striking. The membrane and villi are seen to be the sites of numerous aggregations of inflammatory cells of the small round type, which often form rounded masses situated around the blood vessels. The villi are highly vascular in the early stages, but later endarteritis obliterans may occur, so that the fringes in consequence become fibrotic.

There is also an increase in the number of the ordinary connective-tissue cells (synovial cells) which line the villi. This increase may be so great that in many places the synovial cells may be disposed in many layers. Occasionally polymorphonuclear leucocytes may be observed in some of the more acute types, together with extravasated red blood corpuscles. Fisher's most recent work (27), also describes in rheumatoid arthritis, giant cells of the Aschoff type. These are histiocytes which have two, three or even more nuclei. These cell collections resemble, therefore, the Aschoff bodies seen in the heart. Allison and Ghormley (28) have recently described a specific lesion consisting of peculiar clumps of lymphoid cells not encountered

in any other form of chronic arthritis. These occur in addition to the chronic granulation tissue.

Neumann (29) first described the presence of a substance in the synovial membrane which has the appearance of fibrin, but is in reality a form of degeneration of the connective tissue. Kling and Grzimek (30) state that it gives the fibrin staining reactions for the most part. This is called fibrinoid degeneration. The degeneration affects principally the collagenous connective tissue bundles and forms a striking histological picture. Dawson (31) states that with Masson's trichrome stain it presents a fibrillar structure, which stains a brilliant red, in striking contrast to the vivid green of normal collagen. This degeneration is a characteristic feature of rheumatoid arthritis.

Another interesting and important feature usually noticed at operation is edema of the synovial membrane.

In the seous type, the membrane is comparatively smooth, but the microscopical features are very similar. In the adhesive type enlargement and multiplication of the synovial villi is not a prominent feature, but cohesion of opposed layers of synovial membrane occurs; not infrequently, the latter contracts

adhesions to the articular cartilage, and the joint cavity may be traversed and subdivided by such adhesions. By organization of the inflammatory products in the capsule and synovial membrane, fibrous tissue is formed, which, as it contracts, may bring about various deformities. The ankylosing type is naturally more apt to occur when the affected joint is kept at rest and no attempt made to prevent deformity. The formation of fatty fringes may sometimes be noted, but cartilage and bone develop but rarely in the synovial fringes in this variety. The synovial pannus shall be described in the following.

2. Changes in the articular cartilages and  
in the subjacent bones.

Although these changes occur early, they are usually subsequent to synovial membrane changes. The process may start simultaneously in the synovial membrane and in the cancellous spaces beneath the articular cartilage. In rare cases, changes in the cancellous spaces may precede and be quite advanced before the articular cartilage is appreciably affected. First there are altered staining properties of the cartilage matrix, combined with irregular areas of cartilage cell proliferation.



There is a gradual spreading inwards of a layer of connective-tissue or pannus upon the surface of the articular cartilage. This pannus originates from the synovial membrane at its junction with the articular cartilage and slowly creeps over the surface of the cartilage towards the center of the joint. The pannus is highly vascularized resembling granulation tissue. The deeper layers of the pannus gradually invaded and replace the altered cartilage. The normal smooth cartilaginous surface becomes replaced by a layer of connective-tissue which not infrequently contains nodular areas of newly formed cartilage.

Important changes are to be seen in the cancellous spaces immediately subjacent to the deeper layers of the cartilage. There is a proliferation of the connective-tissue cells of the marrow associated with the formation of new blood-vessels and accompanied in many cases by aggregations of lymphoid and plasma cells. There is an increase in the number of the osteoclasts, and, in many cases, the latter actively attack the original osseous trabeculae so that the cancellous spaces are enlarged by resorption. Osteoblasts, soon or later, lay down new bone upon the surface of the original trabeculae, which may actually

become thicker and denser. This thickening and sclerosis are largely secondary or compensatory as they are seen where cartilage has disappeared or where movement and weight bearing have been maintained.

Processes of very vascular connective-tissue with an advance guard of osteoclasts erupt through the sub-articular bony lamella, invade the zone of provisional calcification and actively attack the articular cartilage from its deep aspect. There is a repetition of the process already described in the more superficial layers of the cartilage. The matrix is dissolved, the cartilage cells disappear, and are replaced by a new formation of connective-tissue, cartilage or bone. The invading vascular connective-tissue meets and merges with that derived from the synovial pannus, and islands of necrotic or degenerate articular cartilage may often be seen surrounded by this newly-formed connective-tissue. The degenerate articular cartilage is eventually replaced by a layer of connective-tissue. The process is not regular and uniform. The articular cartilage usually degenerates in patches, and as these patches are replaced by fibrous tissue the articular surface may assume an irregular appearance. The degenerate articular cartilage may become worn away be-

fore it can be replaced by connective-tissue and the underlying bone is thus exposed and may become eburnated but this is usually a secondary osteo-arthritic change. When the above mentioned changes occur on articular surfaces in apposition, especially if they are at rest, there is fibrous ankylosis, then cartilaginous and bony ankylosis transformation. In rare cases where movement has been maintained the layer of pannus may ossify and constitute an articular surface beneath which the remains of the original cartilage may be seen.

Atrophy. -- Even in the earlier stages there is increased permeability of the epiphysis to the X-rays, particularly in the region of the articular cartilage. This is probably caused by absorption of calcium salts. There is later a diminution in the number and size of the osseous trabeculae and replacement of the marrow by adipose tissue. The bones at post-mortem are extremely light and friable, crumble under the examining finger and the cancellous tissue contains excess fat.

No fundamental difference exists between the gross and microscopical changes in this condition and those seen in certain other forms of subacute or chronic arthritis caused by known infective agents

such as the gonococcus.

Synovial Fluid. -- The exact number of cells occurring in synovial fluid is not too definitely known and figures vary widely. Mc Ewen (32), in 1935, in a study of normal synovial fluids concluded there occurred 10 to 200 nucleated cells per cubic millimeter. Of these 90-95 per cent are phagocytic cells resembling monocytes of the blood or macrophages of probable connective-tissue origin.

The cytology of 52 synovial fluids from 31 patients was noted by Collins (33) to be as follows: total nucleated cells 5,060 to 56,000 (av. 20,170) per cu.mm.; differential count (%) polymorphonuclear 41 to 95 (av. 80); lymphocytes 3 to 45 (av. 16); monocytes 1 to 14 (av. 3); macrophages 0 to 3 (av. 0.3); synovial cells 0 to 3 (av. 0.4). The total protein per cent was 2.7 to 8.5. The polymorphonuclear count depends on three factors: depth of the inflammatory process within synovial tissues, extent of synovia involved, type of inflammation present-acute, subacute, or chronic.

The Subcutaneous Nodule. -- Subcutaneous nodules have been detected in rheumatoid arthritis cases ranging in from seven to twenty-nine per cent of the patients studied by Dawson (34), Clawson and Wetherby (35). Collins (36) has failed to observe nodules of this type in any other than the rheumatoid form of chronic arthritis. The nodules vary in diameter from less than 5 to more than 30 mm. They are hard and painless, the skin moves freely over them, and they usually lie between skin and bony prominences. Mechanical injury plays a part in determining their occurrence, location and chronicity. Nodules may persist for many years but many of the smallest undergo resolution or cicatrization and cease to be demonstrable.

The essential pathology of these structures is a combination of proliferation and degeneration of connective-tissues, accompanied by new formation of vessels at the margin of the lesion and by infiltration with lymphocytes and plasma cells. Collins (36) believes, contrary to the interpretation of others, that proliferation of fibrous tissue and of primitive connective tissue cells precedes degeneration, which then commences within the new tissue at a point usually remote from the vascular supply. The degeneration may

be described as "fibrinoid" and takes the form of a granular eosinophilic swelling of the ground substance, disappearance of nuclei and fibrinous exudation into the tissue spaces. From this nidus the necrosis spreads outwards and may quite soon extend over a large area and engulf other structures such as blood vessels and collagen bundles. A peculiar form of cell reaction takes place around the focus of necrosis, which lends a highly characteristic appearance to the lesion in rheumatoid arthritis. This consists of a wall of radially arranged, closely packed fibroblasts. Vascular granulation tissue of the usual inflammatory type and polymorph invasion of the tissue are not found. Later changes consist of liquefaction of the necrotic material, sclerosis of the encircling fibrous tissue and, in nodules of many years' duration, the formation of fluid containing cysts lined by a concentration of connective tissue cells comparable to a primitive type of synovial or bursal lining.

The gross nodule increases in size not only by the growth of a single necrotic focus and the cell reaction around it, but also by the aggregation of separate foci individually formed by the same processes of proliferation and degeneration. Very frequently early and late stages in the development of these foci may be found

side by side in the same piece of tissue.

As regards the bacteriology, Collins (36) found aerobic cultures of pieces of tissue in ordinary media were sterile, a result in accordance with the experience of Dawson, Olmstead and Boots (37), (38), who also used a wide variety of media and attempted anaerobic cultivation. Clauson and Wetherby (35) grew an indefinite type of streptococcus in 12 out of 17 cases.

**Incidence.**



## INCIDENCE

Rheumatoid arthritis is the most prevalent of the chronic arthropathies and is twice as common in females as in males. Most arthritic clinics find that two-thirds of the patients have this type of arthritis. It is essentially a disease of young people, the average age of onset being thirty-five years. The disease is rare in children occurring in 3 per cent or less of patients of all ages. The peak incidence in the cases of Dawson and Tyson (39) was between February and April. It is much commoner in the temperate zone than in tropical or subtropical climates. Winter produces its harmful effects by coldness plus dampness. The patient's resistance is lowered by overheated houses and excess clothing, by the greater incidence of colds and tonsillitis which may provoke the disease and by a lack of adequate exercise and sweating. The influence of heredity is obvious: the disease appears in grandmother, mother, and daughter. In Dawson and Tyson's (39) series the familial incidence was 15 per cent.

Symptoms and Signs Are  
Characteristic.

### SYMPTOMS and SIGNS ARE CHARACTERISTIC

Often the rheumatoid arthritis patient can date the onset of symptoms from some disturbance of his physical equilibrium such as an acute infection, exposure to cold, a surgical operation, fatigue from over-work or an emotional strain. Mc Crae (40) has found the onset to be acute in about 40 per cent of the cases, and is characterized by sudden pain and swelling of several joints; although the onset may be gradual. There may be fever, headache, and general malaise. Well marked constitutional symptoms make it quite evident that the arthritis is only part of a general systemic disease, according to Poynton and Schlesinger (41). Frequently these symptoms may precede the inflammatory changes in the joints.

Loss of weight, fatigue, anorexia, nervous irritability, vasomotor disorders of the peripheral circulation and tachycardia are amongst the earlier manifestations; the nourishment of the skin also suffers, erythematous rashes may appear, the hair loses its lustre, and the muscles and bone show signs of atrophy. One of the most striking features of the disease is the migratory character of the symptoms,

first one joint and then another being affected. The knees and fingers are the joints most frequently involved first, though other large joints, particularly the shoulders, elbows, wrists and ankles often suffer early in the disease. In the fingers, one sees a pod-shaped swelling of the first phalangeal joints; in time all may be involved and as in all the joints contraction of the inflammatory tissue takes place, also with contraction of the tendons there may be subsequent ankylosis and bizarre deformity by lateral deflexion, hyper-extension, shortening, etc.

The typical arthritic presents certain constitutional signs that are striking. These patients are usually anemic; many of them appear chronically ill and undernourished; some are markedly emaciated. A few patients have excellent nutrition and no anemia.

The tonsils, if infected, may be large, red and full of pus; although they are often small, congested and partially buried. The tonsils may contain deep crypts and the fauces may be infected and present a congestive cyanotic appearance. There may also be a granular pharyngitis with hypertrophy of the lymphoid tissue.

The gums may be the seat of various grades of

gingivitis. Pyorrhea may be localized or general. Apical abscesses are often revealed by the X-ray. Chronic sinusitis is present in many cases.

The examination of the chest is generally negative except in those who give a history of rheumatic fever. Here cardiac lesions may be present. Abdominal pathology may be present in the gall bladder as an infection or other intestinal tract infection. The genito-urinary exploration of the male may reveal a swollen, boggy, and tender prostate. In the female, erosions may be found in the cervical mucosa.

Diagnosis Depends Upon Several  
Differentiating Factors.

## DIAGNOSIS DEPENDS UPON SEVERAL DIFFERENTIATING FACTORS

Rheumatoid arthritis represents a multiple arthritis which seems to be part of a response to a generalized infectious process. The diagnosis of a typical case presents very little difficulty. Cecil (42), (43) points out the following important features in diagnosis:

1. Its tendency to occur in young adults, though it may occur at any age.
2. The migratory character of the joint symptoms is characteristic, particularly in the early stages. Later on, the changes in the joints become chronic and persisting.
3. The affected joints usually are swollen and tender. In mild cases there may be an entire absence of swelling, but as a rule, some degree of infiltration is present.
4. Infectious arthritis is very prone to attack the metacarpophalangeal and proximal phalangeal joints, with the production of fusiform fingers.
5. Foci of infection usually can be demonstrated and are most likely to be found in the throat, sinuses or teeth.

6. In severe cases that are not checked, more or less deformity and ankylosis eventually take place.

Boots (44) states that numerous authors since 1907 have described rheumatoid and osteoarthritis as entirely separate and distinct diseases but this distinction was not held by the majority of the medical profession, especially among those in this country. Recently this clinical differentiation has been confirmed by the laboratory, and there has appeared a renewed interest in it, resulting in a more general acceptance of this view. Extended examinations and observations over a period of time are necessary before one can be certain of diagnosis. Rheumatoid arthritis may occur in the elderly, and the patient may not be anemic, thin, and the joints involved may not be symmetrical. Also, osteoarthritis may occur in thin anemic adults. The diagnosis is equally difficult in very early cases of rheumatoid arthritis before typical fusiform fingers develop and before the streptococcus agglutination test becomes positive and roengenographic changes occur. Further complication is added when osteoarthritis is superimposed later in life on an already existing rheumatoid arthritis, or vice versa. A diagnosis should not be made on one fea-



ture alone, but only after a careful study of the patient and viewing the entire picture.

Perhaps the most significant laboratory finding is the presence of streptococcal agglutinins in the blood serums of patients with rheumatoid arthritis. These are never present in the blood serums of patients with osteoarthritis. They were first reported by Cecil, Nicholls, and Stainsby (45) and this work has been confirmed by other workers including Dawson, Olmstead, and Boots (46), Mc Ewen, Alexander, and Bunim (47) and others.

The determination of the sedimentation rate of erythrocytes is now a routine procedure in all arthritis clinics. It is an aid in diagnosis. Active cases of rheumatoid arthritis have increased values usually exceeding 30 m.m. in one hour. The severity and extent of the arthritic process parallels the sedimentation rate Rawls (48). As the patient becomes worse the rate increases, with improvement the rate returns to normal. In osteoarthritis, the sedimentation rate, while occasionally slightly elevated, rarely attains values greater than 20 or 30 m.m. in one hour. Dawson (49) and Rawls (51) advocate the importance of this procedure in arthritic patients.

Studies recently made by Hartung and Bruger (50) show that the plasma cholesterol tends to be low in rheumatoid and high in osteoarthritis. Increased blood cholesterol occurs in the aged, but Hartung believes that the readings present in osteoarthritis are higher than can be accounted for by age alone.

For the sake of conciseness, the essential features in the differential diagnosis, both from clinical and laboratory standpoints, are arranged in tabular form on the next page. This is a revision by Boots (44) of a tabulation published by Dawson, Sia, and Boots (49) in 1930.

	CLINICAL DIFFERENTIATION	
	Rheumatoid Arthritis	Osteoarthritis
Geographic Distribution	Most common in temperate climates; rare in the tropics.	Climate not much of a factor.
Family History	Usually a history of rheumatic fever or rheumatoid arthritis in an immediate member of family.	Frequently a history of a similar form of arthritis in one or both parents.
Past History	Occasionally a history of rheumatic fever, frequently of tonsillitis or sinusitis.	Not characteristic; sometimes a history of trauma or faulty body mechanics.
Age at Onset	Any age; over 80 per cent between twenty and fifty.	Rare before forty. In women most common at menopause (Menopausal Arthritis)
Mode of Onset	Rarely acute; usually subacute or insidious; often accompanied by migratory pains.	Insidious; not accompanied by migratory pains.
Patient's General Condition	Usually undernourished, anemic, and "chronically ill". Frequently slight fever (99) and slight leucocytosis.	Well nourished, frequently obese; not anemic. No fever, no leukocytosis.
Joint Involvement	Symmetrical and generalized; proximal interphalangeal joints especially involved.	Usually weight bearing joints, spine, hips, knees. Exception, distal joints of fingers, Heberden's nodes.

Appearance of Joints	<p><u>Early:</u> Periarticular swelling, fusiform fingers.</p> <p><u>Late:</u> Ankylosis, extreme deformity, ulnar deflection</p>	<p><u>Early:</u> Slight articular enlargement.</p> <p><u>Late:</u> More pronounced articular enlargement; ankylosis slight and never complete; Heberden's nodes.</p>
Muscular Atrophy	Often marked, particularly in later stages.	Not characteristic.
Cutaneous Changes	<p>(1) Extremities frequently cold and clammy; skin atrophic and glossy; redness of thenar and hypothenar eminences.</p> <p>(2) Psoriasis occasionally present.</p>	No characteristic features.
Subcutaneous Nodules	Present in 15-20 per cent of cases.	Not present.
LABORATORY DIFFERENTIATION		
Agglutination Reaction With Hemolytic Streptococci	Positive in over 50 per cent of typical cases.	Never definitely positive.
Sedimentation Rate	Usually greatly increased; tends to return to normal as patient improves.	Normal or only slightly increased.
Roentgenologic Findings	<p><u>Early:</u> Osteoporosis, periarticular swelling and joint effusion.</p> <p><u>Late:</u> Narrowing of joint space, bone destruction, ankylosis, and deformities.</p>	<p><u>Early:</u> No osteoporosis; slight lipping at joint margins.</p> <p><u>Late:</u> Marked lipping, osteophytes.</p>

## **The Problem of Etiology**

## THE PROBLEM of ETIOLOGY

There are many theories as to the cause of rheumatoid arthritis. Any theory which attempts to explain rheumatoid arthritis must account for the essential and characteristic lesions of the disease, that is, synovitis and periarticular tissue changes. Myers (52) divides the present day concepts of etiology into three main theories. They are, first, the unitarian; second, the so-called "eclectic"; and third, the infectious theory.

The unitarian theory presupposes that both rheumatoid and degenerative arthritis are caused by the same etiological agent or agents and that the factors which determine the type of lesion seen are secondary, such as trauma, foci of infection, the involutional changes of the menopause, and the habitus of the patient. The foregoing factors are thought to cause pathological joint changes characteristic of both types of lesions and thus give rise to the so called "mixed arthritis". Keefer (53) denies the basis of the theory because if a patient with degenerative arthritis develops rheumatoid arthritis, then the lesions of both will be present.

The proponents of the eclectic theory rely upon such terms as "imbalance" and "dysfunction" of the nervous system, the gastro-intestinal system, and the peripheral vascular system. Many workers question just how such "dysfunction" produces chronic inflammatory changes in the synovial membranes and the periarticular tissues. In the gastro-intestinal system gastric anacidity, atonic dilatation of the colon and carbohydrate indigestion are frequently ascribed etiological significance. Bloomfield and Keefer (54) and again Miller and Smith (55), as far back as 1926 pointed out that gastric anacidity occurred no more frequently in patients with chronic arthritis of any sort than in a control group of patients of comparable ages. The question of colonic abnormalities has been carefully reviewed with adequate series of controls by such workers as Bauer (56), Archer (57), Nissen (58), and Haft (59), all of whom found that whatever abnormalities are present are in no way related to rheumatoid arthritis unless as a result of prolonged illness. Colonic abnormalities were neither caused nor influenced by diet. Carbohydrate indigestion is by no means limited to patients with chronic arthritis.

The possible relationship between disturbances

in the peripheral vascular system and the etiology of rheumatoid arthritis is based on such things as the presence of cold hands and feet, increased sweating, abnormal response to cold, decreased capillary circulation in the nail beds, delayed removal of sugar from the blood and improvement of symptoms following procedures which produce vasodilatation. On histological examination of the periarticular and synovial membranes in rheumatoid arthritis, one is impressed by the large blood supply and multiplicity of open capillaries. There seems to be no vasoconstriction present in the periarticular vascular tissues of involved joints. Myers (52) questions etiological relationship of vascular origin because of the infrequency of rheumatoid arthritis in such conditions as thrombo-angiitis obliterans, arteriosclerotic occlusions, Raynauds' syndrome and scleroderma. The studies of the sugar tolerance curve in afflicted patients have been unconvincing because of lack of due regard to age, state of nutrition, amount of sugar ingested, variation in the curve and variation between arterial and venous blood sugar curves.

Recently the role of the sympathetic nervous system in the etiology of rheumatoid arthritis has



received attention because of the treatment by sympathectomy. It is well to point out that all patients with rheumatoid arthritis do not have vasomotor disturbances, even late in the course of the disease. It is rather difficult to understand how vasomotor reactions can produce inflammatory changes in the synovial membranes. Rheumatoid arthritis has not been completely arrested in patients who have had sympathectomies. It would seem rather that the vasomotor phenomena contribute to the symptomatology than that they play a role in the cause of rheumatoid arthritis.

The infectious theory, or rather theories, are based on the presence of slight fever, leukocytosis, increased erythrocytic sedimentation rate, the inflammatory nature of the lesions of the synovial membrane and periarticular tissues, enlargement of the lymph nodes in the region of the joints, and the characteristically exudative nature of the synovial fluid.

To accept the theory of infectious origin one implies that the disease is secondary to focal infection. Adherence to the infectious theory implies that one establish first the existence of a focus of infection, secondly, the capability of this focus to disseminate toxin or organisms, and thirdly, that

the damage to the joints has resulted from such a dissemination of bacterial or bacterial products.

It is necessary to find organisms in the joint tissues or synovial fluids if the condition is a metastatic lesion from a focus or infection. Billings (60) in 1912 called attention to focal infections and their etiologic relations to arthritis. In 1914 Rosenow (61) was able to isolate the *Streptococcus irridans* from the enlarged lymph nodes of these patients. Blood culture studies were also made by various workers to support the metastatic theory. Moon and Edwards (62) in 1917 reported non hemolytic streptococcus from the blood cultures in about 20 per cent of 83 cases. Richards (63), in 1920, claimed 15 positive blood cultures in 104 cases and 4 positive joint cultures in 54 cases. Hadjopoulos and Burbank (64), in 1927, obtained a streptococcus from the blood in 10 per cent of 145 cases studied. Forkner, Shands, and Poston (65), in 1928, cultured streptococci from joints in 16 per cent of 63 cases. Cecil, Nicholls, and Stainsby (66) in 1929 obtained positive streptococcus blood cultures in 96 per cent of 154 cases studied with positive joint cultures in 33 cases for the same organism and in 1931 (67) obtained both blood and joint cultures which were

agglutinated by a high titer of the patient's blood. This led to further study of blood sera.

The indirect method of approach by the study of the blood serum for the presence of agglutinin to streptococci has been used by many workers. A positive discovery in patients with chronic<sup>arthritis</sup> is rather good evidence that these subjects have undergone a streptococcal infection. Dawson, Olmstead, and Boots (68) in 1931 showed that agglutinin present in rheumatoid arthritis blood agglutinated hemolytic-streptococci. In 1936 Mc Ewen, Alexander, and Bunim (69) obtained positive results in as many as 86 per cent of their arthritic patients.

Hadjopoulos and Burbank (70), in 1936, in a study of biopsy material from 21 joints concluded that atrophic arthritis is caused by a multiple mutant infection - at first by a streptococcus which gradually changes into a diptheroid, staphylococcus, or "Micrococcus sarcina". This may explain why sera of arthritic patients frequently react to a variety of apparently unrelated organisms.

Some workers as for example Crowe (71) holds that rheumatoid arthritis is associated with staphylococcal infection. Eagles and others (72) in 1937

believe, by the study of aspirated arthritic joint fluids, they have demonstrated a virus and were able to agglutinate it with the patients' sera agglutinins present.

Stabler and Pemberton (73) in 1937 in a study of a series of patients have found that greater numbers of bacteria occur in the stools of rheumatoid arthritis patients.

It has also been postulated that the reactions in the joints are the response to toxic products or a hypersensitivity to products of organisms. Joint disease occurs commonly in serum sickness, asthma, and hay fever -- this supports the allergic theory. Skin sensitivity occurs in 70 to 80 per cent of rheumatoid arthritis patients for the hemolytic streptococcus. Those failing to show skin reactions may have periarticular tissue sensitivity to the antigen. The foregoing factors suggest rheumatoid arthritis is an infectious disease.

**The Present Status of Trearment.**

## THE PRESENT STATUS of TREATMENT

Atrophic arthritis is a generalized systemic disease requiring individualized treatment. Pember-ton (74) states that it is no more a disease of the joints than typhoid fever is a disease of Peyer's patches. Although there is no specific remedy, enthusiasm and optimism must be exhibited and a number of therapeutic resources must be available or the patient will catch the air of futility with resultant serious depression. There are at the present time several procedures concerning arthritic patients, which at the discretion of the physician, may be applied with advantage to the patient. The following topics represent the current thought concerning such procedure.

Management of foci of infection. -- Many men such as Irons (75) and Westcott (76) regard the elimination of foci of infection the measure of first importance. Some believe that too much is expected by simple removal of foci, especially when irreparable cartilage damage is already done. The tonsils, teeth and sinuses are usually primarily dealt with; but present day writers regard the nasopharynx, cervix,

prostate and even the gall bladder as being very important foci.

Vaccines. -- Many workers such as Wyatt, Hicks, and Thompson (77) note definite improvement in patients by the use of streptococcus vaccines. Autogenous vaccines made especially from nasopharyngeal bacteria have proven beneficial even in very small doses. These vaccines are made from staphylococcus or the streptococcus or from both cultured from various foci.

Foreign Protein. -- Forty per cent of the patients receiving three to five injections given once every other day of the triple typhoid vaccine injections have been entirely relieved of pain and tenderness. Within a month 50 per cent of those relieved had a return of the disease after several months. A few had no recurrences in five to ten years. These are the results of 20 years experience noted by Miller (78).

Venom Therapy. -- Kroner and others (79) in a study of 100 patients treated with an injectable form of bee venom (Apicosan) were impressed with the definite improvement in the clinical symptoms and the significant drop in the corrected sedimentation index in a large percentage of the patients. They conclude that bee venom is worthy of further consideration.

Diets. -- "The patient does best on that diet which would be selected for him if he had no arthritis", Holbrook and Hill (80). A high-calorie, high vitamin diet is prescribed for the underweight patient. Vitamin A, generally as cod liver oil, is considered most useful especially in winter. Vitamin B, in brewer's yeast or wheat germ is generally used. Improvement in some patients has been noted by the use of massive doses of vitamin D.

Sulfur. -- Sulfur (1 per cent suspension in oil) has been used in some cases with improvement, in others results were disappointing. Most workers agree that sulfur is "a forgotten remedy" worth of reinvestigation.

Gold Salts. -- The treatment of arthritis by gold salts was instituted about 10 years ago. British writers now speak of it as very valuable. Some Americans claim it is the most important form of treatment. The mode of action of gold in arthritis is unknown. The dosage and number of courses of intramuscular injections are as yet disputed. Many feel incompetent to handle the drug to the advantage of the patient.

Vasodilators: Histamine, Choline. -- Patients with early atrophic arthritis complicated by vasomotor changes did best when they received subcutaneous injections of



histamine acid phosphate. Eastwood (81) believed the results were analgesic and psychologic but not curative. Transient relief from pain, stiffness, and vasomotor changes were noted. There have not been sufficient results with choline to warrant its use.

Rest and Movement. -- Rest has been called the keynote of therapy, the inevitable price of recovery. Bed rest is necessary for the fatigued body as well as the joints. Inflamed joints should be put at rest in light plaster casts or splints. Rest is vital when joints are markedly inflamed, but as inflammation subsides rest for joints must not be complete lest permanent fixations occur. Active and passive painless motion must be encouraged and increased as possible. Ghormely (82) reminds us that synovial pannus grows over parts of the joint which are not in contact; if motion can be preserved, prevention of the growth of this pannus may be partially accomplished.

Physical Therapy. -- It is said that the systemic phase of the disease has been over emphasized and adequate treatment of the joints has been neglected. Many millions are spent with quacks and irregulars licensed by the states to practice the physical methods too many physicians ignore. Arthritic patients should be taught

home physiotherapy. There should be suitable methods formulated for the patient consisting of simple apparatus for heating, methods for passive, assistive and corrective exercises, and adequate massage. Hydrotherapy is very good whether it be accomplished at a spa or in the home bath tub. The ordinary hot bath at 100° to 120°F. for 20 to 40 minutes is the most useful form of heat. Faradic currents help to control muscle wasting. Short wave and ordinary diathermy are useful in arthritis and beneficial effects have been noted in a few cases. *Ionization*

Fever Therapy. -- The effects of fever therapy have been disappointing. Of cases thus far trying such treatment, 15 to 30 per cent were improved, none became symptom free and most were just temporarily relieved.

Sympathectomy. -- In those cases with muscle atrophy and cold, clammy extremities, sympathectomy is often followed by a degree of comfort because of the warm, dry legs and feet. No obvious change was noted in the appearance or in the degree of movement of the affected joints. The operation is recommended only to improve circulation per se in cold moist extremities. Those following the procedure of sympathectomy from the start feel that clinical results are

disappointing. Deformities, contractures, and ankylosed joints may not be altered in any way.

Prevention and Correction of Deformities. -- There are many well-known procedures for the correction or prevention of deformities. These include the use of plaster splints and braces, and various operative procedures. Deformities may be prevented by early treatment. Adhesions may result from too little or too much motion of the joints, from uncorrected edema, and from joint manipulation or over strenuous physiotherapy. Oxygen insufflation or inflation has successfully been used by Henson (83) to prevent adhesions. When the range of motion is increasing, one should trust to active motion; when it is not increasing, then only should passive movements be carried out, but not forcible manipulation. For the correction of flexed knees some believe posterior capsulotomy often necessary in addition to the use of manipulation and bivalved splints.

Relief from Pain. -- Heat applied in any manner gives the patient considerable relief. Acetylsalicylic acid given in moderate repeated doses keeps the patient more comfortable. If the pain present prevents sleep 1/2 grain (0.03 gm.) of codeine sulfate may be given before retiring. Baths are very good and of course the

patient should remain in bed until pain subsides.

Prognosis; End Results. -- According to Pembrerton (84), 75 per cent of arthritis patients should experience great betterment or complete arrest; 20 per cent are more refractory perhaps because of a dominant continued infection; in 5 per cent therapy is of no avail. Of 452 generally "completely helpless" patients with atrophic arthritis discharged from the Robert Brigham Hospital, Boston, about 66 per cent of those living in 1935 were working, and 21 per cent had relapses (85). The commonest diseases complicating convalescent care were arteriosclerosis in 41 cases, nephritis in 22, hypertension in 19, obesity in 17, myocarditis in 16, gonorrhea in 12, rheumatic heart disease in 10. These were 76 deaths; 18 from pneumonia, 13 from myocarditis, 11 from nephritis, 6 "postoperative", and 28 miscellaneous.

## Summary and Conclusions.

## Summary and Conclusions

Rheumatoid arthritis has through the ages left its mark upon animal and man. At the present time, over one percent of the present population suffers with chronic arthritis. The true nature of rheumatoid arthritis was always puzzling to medical men and it was never clearly differentiated from other joint ailments until in the early Twentieth Century.

The disease is readily diagnosed by means of several differentiating clinical and laboratory factors. The patient presents a picture of a chronic progressive multiple arthritis characterized in its earlier phases by soft tissue swelling, and its later phases by some ankylosis and deformity. Implication of the interphalangeal, metacarpophalangeal, and wrist joints is especially characteristic. The synovial membrane and the subcutaneous nodules, when present, show special histological changes. The radiographic evidence is quite typical, and the patient's serum in a large majority of cases will induce an agglutination of the streptococcus hemolyticus. A rapid sedimentation rate of the red blood cells is characteristic.

Some investigators still maintain that atrophic and hypertrophic arthritis are merely phases of the same arthritic process, but most workers disagree to this supposition. Rheumatoid arthritis is now thought to be a general systemic disease and the joint manifestations are simply thought to be one of the factors present. Many factors of the disease, especially the etiology, are as yet unknown. The pendulum can hardly swing farther at the present day than it does from foci of infection as a causative agent. Most workers look beyond the factor of foci of infection as purely the exciting cause. One would say after reviewing recent literature, that much is to be done and much will be done not far in the future for the arthritis patient.

As yet treatment is only palliative and in the experimental stage. Treatment may be too strenuous or over done, but it is well the practitioner have at his command sufficient knowledge to render some relief to the patient and attempt to restore function and prevent deformity. This is accomplished by supervised rest, then movement guided by a regime of physical therapy. It is well to consult an orthopedist

if the practitioner is not skilled enough in the mode of application of splints and casts and the proper method, procedure, and time of the beginning motion. Vaccine therapy and foreign protein therapy have not had sufficient results to warrant their widespread use.

At the present time 75 per cent of patients note relief after treatment, 20 per cent cannot be reasonably helped by any method, and in 5 per cent therapy is of no avail.



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