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Rheumatoid arthritis : recent trends in its study

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RHEUMATOID ARTHRITIS,
RECENT TRENDS IN ITS STUDY...

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University of Nebraska....

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I. INTRODUCTION.....

I. INTRODUCTION

Chronic arthritis is one of the oldest of all diseases (69), and has existed since life has existed in such form as to leave recognizable fossils; perhaps six hundred million years. It has been demonstrated that the history of disease begins with the Paleozoic and Proterozoic periods, one to two hundred million years ago. Fossil remains of the Paleozoic era have yielded abundant evidence of dental caries, pyorrhea-alveolaris, osteomyelitis and fracture as well as rheumatoid arthritis (75). Virchow in 1870 found "cave gout" in a Pleistocene cave bear which is identical with the arthritis deformans found in so many Egyptian mummies (84) and in people of today. A study of ancient Egyptian mummies and skeletons show both atrophic and hypertrophic forms of arthritis. The skeletons cover a period of 3000 years.

It is estimated that arthritis and bursitis exact an annual loss of more than 7,500,000 weeks of work in the United States with a consequent economic loss of more than \$200,000,000 yearly (55).

At the age of 55 or over the incidence is 11 per thousand, from 35 to 54 it is 3.1, from 15 to 34 the incidence is 0.2 per thousand (55).

The American Committee for the Control of Rheumatism adopted the name "Atrophic Arthritis". The British National Committee on Chronic Rheumatic Diseases adopted the title "Rheumatoid Arthritis". The disease is also known as "secondary infectious arthritis", and as "proliferative arthritis" (7).

A need for accurate criteria for the identification of the various forms of arthritis is evident. The term rheumatoid arthritis is very much abused as terminology of a disease is concerned (15). In the past vague joint pains of all kinds have been designated as rheumatoid arthritis (17) (39), yet rheumatoid arthritis is a definite disease entity with well defined pathological changes in the joints and in the subcutaneous tissue when nodules are present (43). Carelessness in terminology is unfortunate when clinical reports of some form of therapy are being made.

II. CLASSIFICATION.....

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The New York City Committee on Arthritis Clinics has a generally accepted classification of arthritis that would be well to be followed:

Classification of Arthritis

- I. Infectional Arthritis
 - (a) Of proved etiology
- II. Probably Infectional; etiology unproved
 - (a) Arthritis of rheumatic fever
 - (b) Rheumatoid arthritis (atrophic arthritis; chronic infectious arthritis)
 - (1) Adult type
 - (2) Juvenile type (Still's disease)
 - (3) Ankylosing spondylitis (Marie-Strumpell)
 - (4) Psoriatic arthritis
 - (c) Arthritis associated with various infections.
- III. Degenerative arthritis (osteoarthritis; hypertrophic arthritis)
 - (a) Generalized; etiology unknown
 - (b) Localized
 - (1) Secondary to trauma
 - (2) Secondary to structural abnormality
 - (3) Secondary to previous infectional arthritis
 - (4) Etiology unknown
- IV. Arthritis associated with disturbance of metabolism
 - (a) Gout
 - (b) Arthritis manifestations of other metabolic diseases

Classification of Arthritis (con'td)

- V. Arthritis of Neuropathic origin
 - (a) Secondary to tabes dorsalis
 - (b) Secondary to syringomyelia
 - (c) Secondary to peripheral nerve lesions
- VI. Miscellaneous forms
 - (a) Arthritis of serum sickness
 - (b) Arthritis of hemophilia
 - (c) Intermittent hydra-arthritis.

III. ETIOLOGY.....

III. ETIOLOGY

The opinion is current in the literature that the rheumatoid state is a general systemic change from the normal during which any one of several diseases may appear (77). The most common ones to occur are Sydenham's chorea, acute rheumatic fever, rheumatoid arthritis, non-articular forms of joint disease and glomerulo-nephritis. The fundamental deficiency is thought to be nutritional, endocrinal, or both and the exciting cause the streptococcus (79).

Most cases of rheumatoid arthritis first appear from one to six weeks following a local infection, the most common of which is a sore throat. The fact that chronic progressive infectious arthritis is preceded by an acute arthritic infection in 60 per cent of the cases, indicates that a continuity of the process must be presented; the peculiarity of the infectious process must be attributed either to the kind of pathogenic agent or to the reactivity of the individual or to both according to Maliwa (63). The answer to the cause of the arthritis is found in the

difference between two individuals, one of whom completely recovers from a local throat infection, and the other who does not recover but develops arthritis. In the case of the one who does not recover the streptococci remain in the throat and naso-pharynx and at some later date absorption of their products or the bacteria themselves cause the synovial membranes of one or more joints to become inflamed and exude fluid.

Eagles and others (29) believe a virus to be the etiological factor. Crane (24) believes rheumatoid arthritis is definitely associated with a staphylococcal infection.

Synovial fluid carries nutriment to avascular cartilage and since glucose can reach concentrations in the joint fluid even greater than in the blood (76) the way is open for access from the intestinal tract to the joint fluids of other soluble substances, including toxic material or normal materials in excessive amount.

The systemic difference in two people is considered by some to be an expression of immunity in the one and hyper-sensitivity or allergy in the

other. In this connection it is well known that streptococci can and do produce immunity and that they are destroyed in the body by phagocytosis. Schlesinger (87) states there is the possibility that the specific histological changes that occur in uncomplicated rheumatic disease are due to an allergic phenomena associated with a focus of streptococcal infection or perhaps due to a virus.

The theory of focal infection was first invoked by Frank Billings (8) as an explanation for the pathogenesis of rheumatoid arthritis. Billings and most of the earlier writers on arthritis failed to differentiate clearly between infectious and rheumatoid forms of arthritis.

The earlier students of focal infection emphasized the frequency with which streptococci were recovered from focal infections and from this they made the inference that rheumatoid arthritis was probably a streptococcal disease (83). This theory was popular for years, but as a result of negative findings in recent studies it is probable that the streptococci recovered in earlier studies were contaminations.

Cecil and Angevine found in a survey of 200 cases of rheumatoid arthritis that 70 per cent of the patients revealed no demonstrable focus of infection (14). Even when the foci of infection were present their removal seemed to have no permanent beneficial effect on the course of the disease. In no case was the course of the disease arrested or the patient cured. There is a type of infectious arthritis, not rheumatoid in character which is related to focal infection and which is benefited by the removal of infected foci. In this type one or more large joints are affected. The patient runs a fever and the picture is not unlike that of rheumatic fever. The symptoms do not yield to salicylates and there are no cardiac complications.

According to Beir (6) even though bacteria in primary foci, when carried by blood or lymph, may cause many diseases of the gastro-intestinal tract through allergy or the elective affinity of Rosenow or by the establishment of secondary foci, it not appears that such disease may also be caused by the direct infection of swallowed pus, and may be a channel of entrance for bacteria and their toxins. Toxins from foci of infection, especially

those in the mouth and throat, may, through arterial spasm, cause the diminished local blood supply. Through sensitization they may cause the initial injury that is followed by the allergic or irritative signs of chronic arthritis; and also may cause the local or general metabolic disturbance. It is known that a greater number of bacteria occur in stools of patients with rheumatoid arthritis (93).

According to Meyer (66) the most important focus which causes nearly all rheumatic arthritides is a chronic phlebitis in the lower extremities. During a long practice which was restricted exclusively to the treatment of venous diseases Meyer could determine time and again that most cases of arthritis were caused by a focal infection in the veins of the leg, and that the other foci merely played a secondary role as the source for a permanent reinfection of the principal focus in the veins of the leg. The importance of phlebitis as a cause for arthritic diseases is demonstrated by the fact that by its removal in cases which did not respond to treatment of another focus, a prompt cure was effected.

Latent phlebitis is usually caused by a bacterial infection. It may be assumed with positiveness that every phlebitis which is not primarily of an infectious nature, becomes infected shortly after its development and becomes an infectious phlebitis. The infection of the veins may occur in an exogenous or in an endogenous manner. The much more frequent endogenous infection is brought about by way of the blood. The bacteria in this case originates from an infection localized in any part of the body, such as, pneumonia, scarlet fever, grippe, typhoid fever, puerperal infection, furuncle, tonsillar abscess and other conditions. Even if the previous history does not contain any of these infections, in the true sense of the word, the endogenous infections may be caused without the existence of primary infectious disease, which may serve as a source, by bacteria which penetrate through the mucosa of the nasopharynx, where bacteria are found constantly.

Latent phlebitis in the lower extremities is one of the most frequent diseases, in general, and the most frequent of all focal infections. Latent phle-

bitis is usually overlooked because it produces no symptoms which directly point to its existence and also because its symptoms are for the same reason interpreted erroneously. (The symptoms of latent phlebitis will be discussed under "Clinical Diagnosis".)

There is the possibility of other foci causing relapses and preventing the cure of a phlebitis. Meyer (65) gives the name of "feeder" to such foci. The most important "feeder" is a chronic latent inflammation in the jugular vein which is very frequent. The diagnosis of chronic latent phlebitis is based on the tenderness of the veins involved and on the possibility of provoking the latent inflammation by the application of hot compresses. Meyer believed hot compresses exacerbate the symptoms and treat jugular phlebitis by leeches (see "Treatment").

Meyer also states that in cases in which astonishing results were observed by the removal of foci of infections, the infection of the tonsils or teeth was of a primary nature and a secondary focus in the circulation had not yet developed. The infection from the tonsils first extends to the jugular vein and causes here a bacterial phlebitis

and a tenderness of the jugular veins may be demonstrated. The word "latent" is employed for the designation of diseases with symptoms which are hardly perceptible and so Meyer justifies himself for using the expression "latent jugular phlebitis".

When the removal of the infected tonsils and teeth does not bring about a disappearance of the latent jugular phlebitis, a secondary focus of infection in the circulation is already involved, which is independent in its effect and operative removal of tonsils and teeth causes a dissemination of bacteria into the circulation and a provocation of the secondary septic focus in the jugular veins which has already become independent.

After a focal infection has developed in the veins of the neck, the infection from here spreads in the circulation, and a new tertiary focal infection develops especially at a site where the conditions for an infection are especially favorable. According to Lubarsch (65), tissues with venous congestion are a site of least resistance. The secondary focus of infection in the jugular veins is therefore a "feeder" for the infection of

the veins of the leg. A healing of the secondary jugular phlebitis may not bring about a cure due to tertiary infection in the veins of the legs. The reasoning is supposed to explain that the latent jugular phlebitis represents the connecting link between the primary focus in the tonsils or teeth and the phlebitis in the veins of the leg. Latent phlebitis in the lower extremities is exceedingly frequent. In exactly the same manner as the jugular phlebitis can be determined clinically by sensitiveness to pressure.

In order to study the actual conditions of latent phlebitis in the lower extremities, pathologic examinations would be necessary, but the pathologists show little interest for this syndrome.

Cecil and co-workers first noticed presence of specific agglutinins for streptococcus hemolyticus in sera of patients with rheumatoid arthritis (15) (16).

The work has been confirmed by Dawson and others (27). The percentage of patients showing a positive reaction has varried according to different observers from 40 to 90 per cent (81), (70). In well-established cases

of several years duration and with active swelling of many joints the percentage of positive reactions should be about 90 per cent (16). Cultures often fail to reveal hemolytic streptococci even in patients who give strangely positive agglutination reaction. This applies to cultures of blood, joints, throat and stools (72). The agglutination reaction may be a non-specific phenomena similar to the Weil-Felix agglutination of the proteus bacillus by serum of patients with typhus fever.

It is a well known fact that arthritis can readily be produced in rabbits by the intravenous injection of almost any strain of streptococcus. Cecil (14) used a strain of hemolytic streptococcus which when injected intravenously in small doses (2.0 cubic centimeters) produced an arthritis in about 85 per cent of the injected animals. Arthritis appeared in one or more joints between the fourth and thirteenth day and often persisted for many months. Using the same organism an attempt was made to create foci at various selected sites. The dose of streptococcus was larger than that used for intravenous injection. Arthritis was produced in only 11 per cent of the animals and

only in those animals from which streptococci could be recovered from the blood stream shortly after injection.

Angevine and Rothband (4) produced experimentally, hemolytic streptococcus arthritis in rabbits which presented a picture very similar to that described by Allison and Ghormley (3). Further experiments showed that a similar picture could be produced in experimental pneumococcus arthritis.

Jordan (51) has shown that when turpentine is injected into synovial tissue of rabbits a lesion can be produced which is indistinguishable from the experimental streptococcal arthritis and quite similar to that seen in human rheumatoid arthritis.

Interest at present is not in the streptococcus group but in the so-called pleuropneumonia-like group of organisms. These organisms have been found to exist in symbiosis with the strepto-bacillus moniliformis.

Findlay has cultivated the pleuropneumonia-like organism from the joint tis-

sue of rats suffering from a type of polyarthrititis. They were able to reproduce the disease in mice by injecting into the foot pads (32).

Sabin states that arthritis can be produced practically 100 per cent in mice when 0.5 cubic centimeters of a 24 hour culture is injected intravenously or 1.0 cubic centimeter intraperitoneally (85). Swelling of the joints may appear as early as 4 to 5 days. The arthritis is migratory, new joints becoming involved while others recede. Puffiness of isolated digits, seen so often in human rheumatoid arthritis, occur frequently in these mice. The process is progressive and chronic in one or more joints, leading often to ankylosis, especially in the knees. Tests revealed that the microorganism does not multiply in the brain, viscera, pleura or peritoneum. Excepting the arthritis, the mice appear in good health and not one of 150 with joint involvement died of the infection.

Pathological changes are limited to the joints, and in the human disease, consist chiefly of proliferation in the synovial membrane, the capsule, the perichondrium of the articular car-

tilage, combined with a synchronous proliferation of the connective tissue and probably endostium of the epiphyseal marrow directly below the joint cartilage. Intracutaneous, subcutaneous, intramuscular or intrathoracic injection or nasal instillation induced neither arthritis nor any local or systemic diseases. Rabbits and guinea-pigs developed neither arthritis, fever or other signs of disease after inoculation with large amounts of culture.

This pleuro-pneumonia-like microorganism passes through a 500 mu but not 396 mu gradocal membrane. This suggests that the size of the smallest unit capable of multiplication is in the same range of magnitude as that of vaccine virus.

In most cases of rheumatoid arthritis one can demonstrate many clinical and laboratory abnormalities which serve as evidence that the disease may be infectious in origin. The majority of workers favoring this theory consider that the hemolytic streptococcus plays an important etiologic role, again without adequate proof. Adherents to this theory are therefore interested in the incidence of upper respiratory infections

preceeding the onset of the disease. A history of such infections is not obtained with any regularity. The failure to elicit more regularly one of the usual precipitating factors necessitates the studying the patient as a biologic unit.

Most physicians who have cared for patients with rheumatoid arthritis have observed temporary relationships between onset of arthritic symptoms and emotional crises (19). In some instances the exacerbations and remissions run parallel to changes in the environmental stress under which the patients live. Such examples carry little weight except with the physician who has seen the phenomenon. He knows that he is dealing with a positive relationship but cannot prove it. It becomes a matter of personal conviction without adequate evidence.

On the hypothesis that free hydrochloric acid acts as a germicidal barrier to the passage of organisms through the stomach to the intestine, many workers have examined the incidence of achlorhydria and hypochlorhydria in rheumatoid arthritis (31). After careful examination of

all the data it has been concluded that the incidence of achlorhydria or hypochlorhydria in arthritis is five times higher than in normal subjects, but only slightly higher than in certain other diseases, the difference being too slight to warrant any definite conclusion being made as to causal connection. Likewise no constant metabolic changes are found in rheumatoid arthritis, primary or secondary (68), (9).

Vague statements on "endocrine imbalance" as a contributory if not primary cause frequently appear in the literature of primary rheumatoid arthritis, but little that is definite is said regarding the exact nature of that imbalance. The pituitary, so far as is known, has no direct influence in the production of arthritis. In so far as it controls through its thyrotropic and gonadotropic hormones the functioning of the ovary and thyroid, it may be said to have an indirect influence on those forms of arthritis in which endocrine disturbance is prominent (52).

In the cases of chronic polyarthritis which have no tendency to remissions, the sensitiveness to adrenalin is decreased, while the

sensitiveness to insulin is occasionally normal according to Buday (11). In the cases which have a tendency to remissions and recidivations, the sensitiveness to adrenalin is normal while the sensitiveness to insulin is increased. A study of the literature shows that rheumatoid arthritis may be associated with either hyper- or hypothyroidism, or with the two states alternating. The obvious inference is that there is no direct causal relation between the thyroid and disease (31).

Chronic vitamin C deficiency in the guinea pig produces an arthropathy with many similarities to rheumatoid arthritis and in certain instances superimposed infection accelerates and accentuates the pathological process (82). The experimental infection in presence of adequate vitamin C failed to produce arthritis. There is little clinical evidence to support the idea that patients with rheumatoid arthritis are suffering from a deficiency of vitamin C and vitamin C in large doses does not cure the disease.

IV. PATHOLOGY.....

IV. PATHOLOGY

Work carried out on synovial tissues removed at operations upon patients suffering from rheumatoid type of arthritis shows definite pathology according to Fisher (34), McEwen (61) and Collins (23). Hippocrates said "the bile mingled with the blood in the veins and articulations, causing a swelling of joints with production of acute pain" (47).

Arthrotomy and lavage have advantages over aspiration since the rheumatoid joint contains a variable amount of necrotic material due to fibrinoid degeneration of the synovial membrane and which is impossible to remove through a needle or trocar. After suitable manipulation of the specimens and high speed centrifugation, suspensions are obtained which are indistinguishable from elementary bodies demonstrable in similar suspensions from recognized virus diseases. Similar bodies have been found in pericardial and pleural exudates and joint fluids from rheumatic fever.

In early cases of rheumatoid arthritis sections of the joint synovial membrane showed

proliferation of the synovial villi and of the specialized synovial cells lining the villi (74). In the deeper layers of the synovial membrane are focal collections of cells which are chiefly perivascular. Allison and Ghormley (3) drew particular attention to the "focal collections of lymphocytes" often observed and claimed that these collections are a specific diagnostic feature.

The cells constituting the collections are lymphocytes and histiocytes and occasionally large histiocytes and resembling the giant cells seen in the Aschoff nodule of rheumatic fever. In the regions of these collections, areas of focal hyaline degeneration of the connective tissue can occasionally be seen which often invade the adventitia of the blood-vessels. Proliferation of the vascular endothelium is a prominent feature. There is complete absence of the polymorphonuclear cells which are a feature in arthritis associated with joint pyogenic organisms.

At a later stage of rheumatoid arthritis a form of degeneration of the connective tissue known as fibrinoid occurs (57).

Perivascular collections of cells are seen and giant cells of the Aschoff type are prominent in both rheumatic fever cases and rheumatoid type of arthritis. At this stage of the disease the synovial membrane is diffusely infiltrated with chronic inflammatory cells, principally lymphocytes, plasma cells and epithelial histiocytes (73).

Fibrinoid degeneration was first described by Neumann in 1880 and in 1896. It is a substance which has the appearance of fibrin but which is a form of degeneration of the connective tissue. Klinge and Grzimek (3), state it gives the fibrin staining reactions.

Fibrinoid degeneration of the synovial membrane is an important feature of rheumatoid arthritis and is not confined to acute rheumatism. In acute rheumatism it is seen not only in the synovial membrane but in the heart and other regions. The degeneration affects principally the collagenous connective-tissue bundles and forms a definite histological picture (25).

At operation the synovial membrane can often be seen to be edematous. Near the surface of the synovial membrane are a large number of clear

areas varying in size. These areas are surrounded by fibrinoid degeneration of the connective tissue and interspersed in this area are large numbers of giant-cells. The giant-cells vary in size; some being of the typical Aschoff variety and having two or three nuclei, while others have many nuclei and resemble foreign-body giant-cells. The giant-cells appear to be destroying the fibrinoid material and many of the smaller spaces appear to be formed in this manner.

The late stages of rheumatoid arthritis show a synovial membrane with lymph-adenoid nodules often with a clear center. The nodules are formed by a perivascular collection of lymphocytes, histiocytes and plasma cells. This is followed by proliferation of the vascular endothelium and the clearer central area contains many cells of the endothelial type interspersed with strands of fibrin. The appearance of these nodules lends support to the tuberculous theory of origin of this form of arthritis.

In later stages the synovial membrane and villi become fibrotic and according to Fisher (33) many of the blood-vessels become blocked. There is

striking development of connective tissue around the vessels in the form of concentric rings (pericapillaritis diffusa). Cecil (12) states that the synovial membrane and the subcutaneous nodules in rheumatoid arthritis (22), (18) (26), presents interesting and characteristic histological changes but that these changes are not absolutely specific for rheumatoid arthritis.

The nutrition of the articular cartilage and entire joint is seriously impaired and this interference with nutrition probably causes the secondary osteo-arthritic changes. Radiological change is striking even in the early stage of the disease. It is dependent on a general loss of bone calcium noticeable throughout the skeleton when the disease is active. This general osteoporosis occurs long before the destruction of cartilage according to Howitt (49). It is only in the late and chronic stages that intra-articular damage is apparent in the form of destruction of cartilage and bone, resulting in subluxation and ankylosis of the joint.

The most important pathological deviation from the normal which is found in true rheumatoid arthritis is a vasoconstriction affecting the cap-

illary circulation. Resultant upon this constriction is a failure of absorption on the part of the tissues, as proved by the fact that the venous blood shows a relatively high saturation with oxygen and low saturation with carbon dioxide. More important is the lowered rate of sugar removal. The arterial and venous blood-sugar curves are approximately the same in rheumatoid arthritis, the vein in many cases containing even more sugar than the artery, whereas normally the arterial-venous difference is considerable. It is fair to deduce that the muscles and tissues of the rheumatoid arthritic patient are unable to deal with the circulation of sugar in the normal way.

Arthritis and the rheumatoid syndrome depend for their local pathologic manifestations, in part at least, on a disturbance in the finer blood supply of the tissues, probably in the capillaries, such that the local metabolic processes are interfered with (76). A secondary disturbance of the acid base equilibrium, at these local sites only, probably plays an important role in the removal and deposition of bony tissue.

The central articular area of joint car-

tilage is without blood supply, and it has not been known definitely whether the synovial fluid can supply pabulum to cartilage. The synovial fluid however is in intimate and active communion with the blood stream and the glucose ingested by mouth reaches the joint fluid from the gastro-intestinal tract with such rapidity as sometimes to exceed in concentration the glucose in the blood according to Pemberton (76). As cartilage is one of the tissues of the body highest in glycogen, it requires an abundant supply of glucose and the means of getting it is obviously at hand.

A change in the peripheral circulation in arthritis was made by Pemberton (76). In his observations the red cell count was lower in the drop of blood first issuing than in subsequent free flowing blood whereas in normal subjects the opposite was more often encountered. Secondary invalidism did not afford an adequate explanation.

The skin over the articulations with chronic involvement is cooler than the surrounding tissues during the intervals between attacks; this symptom suggests the study of the condition in peripheral vessels. Capillaroscopy demonstrates nar-

row capillary loops with granular columns of blood, signs of diminished velocity of the current (63). Such vasomotor disturbances are the expression of a definite biologic condition. A bradytrophic tissue such as cartilage which has no blood supply of its own is particularly sensitive to prolonged nutritional disturbances on account of lack of compensatory processes. These capillary changes have a relation of the patients sensitiveness to draft.

Dawson (25) in his comparative studies of subcutaneous nodules in rheumatic fever and rheumatoid arthritis believes the histo-pathology of the subcutaneous nodule of rheumatoid arthritis differs little, if any, from that of the subcutaneous nodule of rheumatic fever.

The pathological histology of the synovial tissues of rheumatoid arthritis and acute rheumatism presents a similar and specific picture. The similarity of pathological reactions of the synovial membrane supports the theory that they are manifestations of the same fundamental pathological process.

By means of supravital stains McEwen (62), has shown the cells of the subcutaneous nodules of

both rheumatic fever and rheumatoid arthritis are similar. The negative results of bacteriological examination of the joint tissues and fluid in uncomplicated cases together with the absence of polymorphonuclear reaction in the synovial tissues--which is characteristic of arthritis associated with pyogenic organisms--is not in agreement with the idea that the rheumatoid type is due to presence in the joint of streptococci or other pyogenic organisms.

In cases in which streptococci were isolated from synovial membrane, typical pyogenic membrane was observed, intensely infiltrated with polymorphonuclear cells. In these cases secondary infection has been superimposed upon some other factor.

Klinge and Grzimek maintain (57) that rheumatic fever and arthritis of the rheumatoid and osteo-arthritic types are different forms of the same and underlying pathological process.

V. CLINICAL DIAGNOSIS.....

V. CLINICAL DIAGNOSIS

The clinical criteria for the diagnosis of rheumatoid arthritis would be the following (12):

(1) Some of the joints must be swollen, and preferably some one or more of the knuckles or the proximal interphalangeal joints of the fingers.

(2) The disease is practically always polyarticular and tends to remain in the joints already involved as it spreads to new joints.

(3) There is a strong tendency to symmetrical distribution of the affected joints. The typical fusiform finger is the most characteristic feature of the disease.

(4) There is usually evidence of general systemic infection as indicated by slight fever, anemia, and loss of weight and strength. The vaso-motor disturbances are quite characteristic, especially excessive perspiration and rapid wasting of muscles.

(5) The sedimentation rate of the red cells is practically always quite markedly increased (78).

(6) The x-ray appearance of the bones and joints is highly characteristic. One of the ear-

liest changes is the osteoporosis of the bones adjacent to the affected joints. As the disease progresses there is narrowing of the interarticular space and blurring of the whole joint architecture. Small punched-out areas are sometimes seen about the head of the bone adjacent to the affected joint.

(7) The agglutination test with the patient's serum against the streptococcus hemolyticus is positive in 65 to 75 per cent of cases.

(8) In well established cases of several years duration, characteristic ankylosis and deformity of the affected joints renders the diagnosis very simple.

(9) Plasma cholesterol tends to be low in rheumatoid arthritis and high in osteo-arthritis (42).

Among the constitutional findings are: fatigue and mental hebetude. Later atony of the intestinal tract, anorexia, loss of morale, despondency, neuritis and psychic disturbances.

According to the recent work of Meyer (66) and the relation of latent phlebitis to rheumatoid arthritis the symptoms of latent phlebitis according to his work should be discussed. He divides his cases into four groups: (1) General---loss of

energy and fatigue, headaches, feeling of dizziness and a feeling of heaviness in the limbs usually there is a secondary anemia with a relative lymphocytosis; (2) characteristic symptoms in the legs, especially when walking or standing---the first steps in the morning are frequently painful and a frequent complaint of paresthesias in toes and cold feet; (3) compensatory veins---the veins have appearance of varicose veins and are frequently regarded as such. In varicose veins the dilation of the lumen is attributable to a congenital connective tissue weakness, and is caused in compensatory veins by the overburdening of the vessels involved. The inflamed deep veins which are partly occluded by thrombi permit the passage of only a small quantity of blood through their constricted lumen. The principal quantity of blood must therefore flow through the cutaneous veins, which become dilated accordingly. Such compensatory veins must not be removed under any circumstances until the phlebitis of the deep veins have been removed. The differentiation of compensatory veins from varicose veins is easy with the aid of pressure points: (4) tenderness at the characteristic pres-

sure points---a cardinal symptom of the inflammation is the pain, which is increased when pressure is applied to the inflamed tissue. Observations in several thousand cases by Meyer have disclosed that this pressure pain may be evoked almost always at three points of the leg. They are all situated medially from the tibia. The posterior tibial vein in the lower third of the leg is pressed from below against the median edge of the tibia. In the middle third of the leg the pressure point is found directly beside the tibia, and in the upper third about two fingerbreadth's away from it.

VI. PRODROMAL SYMPTOMS AND
EXCITING FACTORS.....

VI. PRODRIMAL SYMPTOMS AND EXCITING FACTORS

There is commonly in rheumatoid arthritis a long history of definite prodromal symptoms (49). On careful inquiry into the early history, it will be found that in childhood they were unduly frail, and prone to all forms of juvenile ailments. In adolescence they were nervous and excitable, and alternated between periods of enthusiasm and depression. Undue fatigue was a noticeable characteristic, and although mentally alert and physically active, they soon became exhausted, listless and irritable. Their vasomotor system was unstable, so that they were susceptible to cold, unable to tolerate cold-bathing, often subject to chilblains or even a Raynaud-like condition of the extremities. They were thin, somewhat poorly developed, and subject to cramp and vague muscular pains.

If such a patient is examined shortly before the onset of joint symptoms, the following syndrome will be found: loss of appetite, tachycardia, a fall in blood pressure, a slightly raised temperature, sweating of the hands and feet, dermatographia, tremor, general nervousness, loss of weight, and an

extreme degree of fatigue disability. These symptoms are referable to over-stimulation of the katabolic group of endocrine glands. It is while in this sensitive state that some exciting factor is superimposed, such as exposure, physical or mental strain, pregnancy or perhaps an intercurrent infection, and then after a variable interval, the familiar joint changes develop. The course of the disease is not continuous, and apparent recovery is common. After a variable interval, however, and particularly if physical strain or mental shock supervene, symptoms reappear with renewed vigor and further advance sets in.

General muscular atrophy is apparent before the onset of the joint changes (59). As this atrophy falls more heavily upon the weaker extensors, the characteristic flexion deformities appear.

Atrophic arthritis is largely a disease of the temperate zone and is much less common in the tropics (45). The incidence is highest in the early spring, and cold, dampness and poor hygienic and environmental conditions unquestionably predispose to its development. It is more common among females than among males. Mental stress, anxiety,

worry and exhaustion apparently have a determining influence (7).

In regard to the familial tendency, certain body types have been found to be most prone to the development of the disease, particularly the slender, flat-chested, hollow-backed enteroptotic build. In 200 cases Strangeways (96), reports a family history of arthritis in 56.5 per cent.

VII. TREATMENT.....

VII. TREATMENT

The therapy of rheumatoid arthritis is empirical and therefore new cures are coming in and continuously and going out.

Sulphur therapy has been attempted on the theory that the cells of an arthritic patient have lost the ability to retain sulphur. Sullivan and Hess (98) expressed the belief that the cystine content of the finger nails of arthritic patients is definitely low, an indication of disturbed metabolism of sulphur.

According to Freyberg (37) there is no important difference in the amount of sulphur eliminated by patients with arthritis as compared to normal individuals. No indication of sulphur deficiency was found in any patient with arthritis. The amount of sulfur eliminated in each urinary fraction was practically identical in the arthritics and controls, except for a slightly higher conjugated fraction in the arthritics. This difference is most likely unimportant; if it is significant, it clearly indicates there is a sufficient supply of sulfur available for conjugation

and that there is no impairment of this detoxification mechanism. There is no biochemical evidence that elemental sulfur or inorganic sulfate injected or ingested can be utilized by the human in the synthesis of sulfur-containing amino acids. The analysis of finger-nails showed no significant changes in the cystine content after sulphur medication.

Abrams (2) concludes that colloidal sulphur even when administered in large doses does not alter the course of rheumatoid arthritis. The uniformity of the results renders them significant. In conclusion the colloidal sulfur therapy represents another antirheumatic remedy which can be dispensed with in the treatment of rheumatoid arthritis with considerable saving of expense to the patient.

The Council on Pharmacy and Chemistry of the American Medical Association has been unwilling to include in its list of approved new and non-official remedies any of the colloidal sulphur preparations now on the market.

Gold therapy for arthritis was first instituted twelve years ago by Forestier (35), but was disregarded by Americans until recently. The mode of action of gold in arthritis is unknown.

Intramuscular injections seem to be as effective as intravenous injections and are probably safer (12). The drug is given in courses in much the same way as bismuth and arsphenamine in syphilis. Begin with 25 to 50 milligrams and work the dose up to 100 milligrams, with a total dosage of 1 to 2 grams depending on how the patient reacts to the drug. Injections are usually given once a week deep into the buttock. Several courses are recommended since relapses and failures result when only one course is administered. Patients on gold therapy should be followed with frequent blood counts, urinalyses and sedimentation tests.

Reactions to gold are numerous and some quite serious and occasionally there are fatal results. Many patients have an immediate vasomotor disturbance which is not serious but unpleasant. The commonest form of toxic reaction is drug dermatitis which appears as a dry scaly itching erythema or morbiliform rash. Occasionally severe exfoliative dermatitis is encountered. Next to dermatitis, stomatitis is the commonest toxic manifestation, showing itself as a loss of taste, sore tongue and gums or an

ulcerative stomatitis. Some patients develop acute gastro-intestinal symptoms with fever, vomiting, epigastric pain and diarrhea. Occasionally acute hepatitis with jaundice is encountered, and rarely acute yellow atrophy. Occasionally glomerular nephritis occurs and finally purpura hemorrhagica, aplastic anemia and agranulocytosis. Some observers believe that toxic manifestations of gold therapy can be avoided by simultaneous injection of calcium gluconate; others recommend liver extract or glucose.

Hartfall and Garland (41), saw gold therapy results almost miraculous on patients showing various grades of disability. They also noted improvement in general health and appetite, gain in weight and reduction in sedimentation rate. Vitamins A, B and especially C given in large doses have been recommended as preventing many of the gold therapy complications (7).

Key and others (53), have given nicotinic acid in doses of from 150 to 300 milligrams daily to patients in whom skin reactions or irritations of the mucous membranes from the gold have developed and with this treatment the lesions im-

proved rapidly, and the patients tolerance to gold seemed to be increased.

According to Howitt (49) the urine should be kept alkaline during the gold treatment. Edgecombe (31), believes gold therapy represents the greatest advance in the drug treatment of arthritis made during the last 30 years and its use in osteoarthritis and in non-articular rheumatic diseases is of no value, but should be limited to primary and secondary rheumatoid arthritis and the complications are reduced by the use of smaller dosage and testing for idiosyncrasy to the drug.

Kling (56), attempted to explain the mechanism of gold therapy in rheumatoid arthritis and concluded that gold belongs to the group of heavy metals and hence shares with them the property of inhibiting bacterial growth in organic material, the so-called oligodynamic effect. On the basis of numerous animal experiments it has been concluded that the therapeutic effect of gold on experimental animals is not due directly to its bactericidal properties, but to a stimulation of the defense mechanism, especially of the reticulo-endothelial system as well as to the effect of the local deposit of gold on the defense mechanism of the synovial

membrane.

Vaccine therapy has lost some of its vogue because of the growing popularity of gold therapy (5). Streptococcus vaccine still has a place in the treatment of rheumatoid arthritis (12), (101). Cecil (13), uses it on those patients who cannot take gold and occasionally it is used in combination with gold. Schallig (86), gave a routine treatment comprised of administration of 0.5 cubic centimeter of staphylococcus-streptococcus undenatured bacterial antigen given intradermally twice a week and only seven patients out of one hundred failed to benefit. Sixty-five per cent of the patients were completely relieved of their presenting symptoms within ten weeks of instituting antigen therapy. An additional twenty-eight per cent required from ten to twenty-five weeks of antigen administration before attaining a favorable result.

Sidel and Abrams (90), compared the results of vaccine therapy with saline injections as controls and concluded that the patients treated with polyvalent streptococcus vaccine intravenously responded essentially in the same manner as the pa-

tients who were treated with saline solution, hence the saline injection therapy is as effective in chronic arthritis as polyvalent streptococcus vaccine.

Selig (89), in his work on the relationship of dental infection to arthritis concluded that because the relationship between cause and effect is not proven radical or ruthless dental extractions should not be done but that radiographically positive dental foci should be removed whether pulpless teeth or root fragments but too much should not be promised the patient. According to Williams and Slocumb (100), if disease of the sinuses is found, an attempt should be made to eradicate it, but too optimistic an outlook as to the results should be avoided but it is definitely an error to assume that the sinuses can be ignored as possible foci of infection in cases of arthritis.

Many authors have expressed their appreciation of the use of non-specific protein injections (75). Typhoid vaccine intravenously in small increasing doses seems to be the most popular form of the use of this type of therapy,

although other foreign proteins have been used with almost equally good results. A large percentage of patients are helped by one or another form of vaccine. If the basal metabolic rate of this type of patient is lowered, small doses of thyroid extract have often given considerable relief. According to Miller (67), forty per cent of patients had relief from pain and tenderness by use of foreign protein but within one month fifty per cent of those relieved had a return of the disease.

A definite improvement in clinical symptoms and a significant drop in sedimentation index was obtained by Kroner (58), and others, in a large percentage of cases by use of bee venom.

Cohen and his associates (20), have treated atrophic arthritis with estrogenic substance, and believe that not uncommonly the menopausal and postmenopausal eras of a woman's life are associated with some degree of arthralgia and whether these changes are directly due to the endocrine readjustment of this period is not known but that they play some part in causation of the arthritides seems obvious. Of the total of eleven patients with active menopausal symptoms, seven

noted improvement in the joint symptoms as well as in the subjective phenomena related to the menopause, while four noted a general improvement with no effect on the joint symptoms.

Muether (71) used histamine in rheumatoid arthritis administered by ointment, subcutaneous injection and iontophoresis, and concluded that histamine diphosphate dilution (1/1000), when properly given to individuals without complete ankylosis of the joints will increase motility and frequently relieve pain. The subcutaneous administration of the drug seems to be as satisfactory as iontophoresis. Histamine will not cure arthritis and is at best an adjunct to other forms of therapy (30). Histamine, although not having a specific therapeutic effect in rheumatoid arthritis when given subcutaneously does seem to be of value in the symptomatic treatment of the disease. It apparently enhances the value of other forms of therapy and, in many instances, enables the patient to carry on activities which would otherwise be impossible. Cohen and Rosen (21) had similar results with mecholyl and histamine on peripheral circulation and

relief of arthritic pain.

Locke and associates experimented with inhaled carbon dioxide in relation to rheumatoid arthritis. A part of the limitation to movement in rheumatoid arthritis is due to muscle spasm and pain, not to limiting changes in structure which can be lessened through administration of carbon dioxide and returned through acceleration of carbon dioxide loss (overbreathing) to a degree suggesting relationship to the phenomenon of hyperventilation tetany. They concluded the possibility that carbon dioxide impoverishment may be a factor in the development and progress of atrophic arthritis and work is under way on the problem of therapy but no conclusive progress has been obtained to date. Harding (40) found arthritic muscles that were atrophied consumed an increased amount of oxygen while muscles atrophied from disuse showed only a slightly elevated oxygen consumption. The more marked the atrophy the greater the increase in knee jerks (80).

Cobra venom has been used in arthralgias by Steinbrocker (94). Pain is the most common complaint in arthritis, neuralgia and related

conditions. These ailments at times may be dominated by discomfort so intractable as to subordinate all other considerations until symptomatic relief is provided for the patient. The benefit recorded from cobra venom refers almost in every instance to subjective relief. In a few cases stiffness and limited mobility were found to be improved along with discomfort. Some of the patients who benefited from venom had their treatment interrupted. Injections of saline solution were substituted without their knowledge, only to be followed shortly by a definite recurrence of previous improved symptoms. There was no noticeable effect of injection of the cobra material on articular enlargement even when the pain was said to have been relieved.

Frazier (36), has done considerable work with physiotherapy and hydrotherapy at a well known spa where the patients were not obliged to pay either for their hospitalization or for professional care. For the hydrotherapy the water was maintained at a temperature of from 90 to 96 degrees Fahrenheit which was not only comfortable

to the patient but also helped considerably to relax the muscles associated with the involved joints thus further facilitating motion and also reducing pain. Frazier concludes that of the gross admissions of chronic arthritic patients fifty per cent left the hospital after an average stay of forty-five days with what both the patient and physician considered worth while improvement. Of those who were given the hydrotherapeutic pool treatments, at least seventy-five per cent left with a like degree of recovery.

Solomon and Stecher (92), report the results obtained by artificial fever therapy with the Kettering hypertherm on patients with atrophic arthritis at City Hospital, Cleveland during the last five years and concluded that the final results obtained were not as satisfactory as were the immediate effects. The final results were determined by the condition of the patients when last seen. The patient's condition on discharge or when last seen was found to be unchanged in eighty-two per cent. In ten per cent it was thought to be improved and in eight per cent it was definitely worse. They further believe that atrophic arthritis characteristically

produces damage and destruction to joints of such a nature as to seem utterly irreparable, and effective therapy should prevent permanent joint changes if sufficiently early in the disease or should prevent further progress of such changes which are already present.

Most physicians give generous quantities of vitamins A, B, C and D as routine therapy of rheumatoid arthritis (82). Dreyer and Reed (28) strongly advocate massive daily doses of vitamin D for treatment of rheumatoid arthritis. The doses of 200 to 250 thousand U.S.P. units a day which are recommended frequently excite toxic symptoms, chiefly nausea, anorexia, lassitude, diarrhea and gastrointestinal pain. Irons (50) objects to this massive vitamin D therapy believing that some permanent injury might be done. Massive vitamin D therapy does not meet with an enthusiastic response from the profession. Slocum and Hench (91), were unable to obtain any benefit from this therapy, and negative results have been reported by Abrams and Bauer (1). According to Holbrook and Hill (48), the patient does best on that diet which he would select if he had no arthritis.

It has been known that an attack of catarrhal obstructive jaundice would produce amelioration in the symptoms of rheumatoid arthritis. In Hench's cases (44), the jaundice was caused by the toxic action of cinchophen, but the patients who had simple catarrhal jaundice expressed similar relief. In the majority of cases, marked reduction of pain and swelling and a striking increase in motion accompanied the more or less complete analgesia, and the rheumatic process appeared to have suddenly become inactive for varying periods, sometimes for days or weeks, occasionally for months or years.

Thompson and Wyatt (99), employed bile salts alone and bilirubin alone without any beneficial effect. Margolis employed autolyzed liver which produced exacerbation of the symptoms. John Davis of the Physiology Department at Corness believes that crude liver extract in large doses has a favorable effect on the course of arthritis.

Arthrotomy and lavage is a valuable means of treatment in carefully selected earlier cases of the disease, which have proved resistant to the usual medical and physical treatment. According to

Fisher (34), many patients have their symptoms completely disappear after arthrotomy and lavage and have remained cured for periods as long as twelve to fourteen years. Oxygen has been injected into affected joints to prevent adhesions (46).

VIII. SUMMARY AND CONCLUSION....

VIII. SUMMARY AND CONCLUSIONS

Rheumatoid arthritis is one of the oldest of all diseases and has existed since life has existed in such forms as to leave recognizable fossils, probably six hundred million years.

The term rheumatoid arthritis also known as secondary infections arthritis, atrophic arthritis and proliferative arthritis. It was formerly a vague terminology and now is a definite disease entity.

Its etiology is still unproved but probably is on an infectional basis which probably will be determined in the near future. Ideas as to etiology have varied from general systemic changes to streptococci, staphylococci, virus and even an allergic phenomena. Focal infection has always been considered as the cause and recently Meyer has extended the focal infection idea to focal infections causing even more significant secondary infections especially chronic phlebitis in the lower extremities. These infected veins of the leg are the actual cause and the primary focus merely reinfects the principal focus of the leg. The infection of the leg veins known as

"latent phlebitis", may occur in an exogenous or in an endogenous manner and is usually overlooked because it produces no symptoms which directly point to its existence. Meyer also attempts to explain the failure of cure of phlebitis to the possibility of other foci causing reinfection which he terms "feeders" of which chronic latent inflammation in the jugular vein is very frequent. Meyer states that in cases in which good results were observed by the removal of foci of infections, a secondary focus in the circulation had not yet developed and likewise a healing of secondary jugular phlebitis may not bring about a cure due to tertiary infection in the leg veins. Perhaps more detailed pathological study of such latent phlebitis would rule out or prove Meyer's work.

To prove that rheumatoid arthritis is on an infectious basis, workers demonstrate that arthritis can readily be produced in rabbits by intravenous injection of almost any strain of streptococcus. Present work by Findlay and Sabin is on the pleuropneumonia-like organisms. They have been able to produce in rats a type of arthritis essentially identical to rheumatoid arthritis in humans.

Pathological changes are limited to the joints and consist chiefly of proliferation in the synovial membrane, the capsule, the perichondrium of the articular cartilage combined with proliferation of the connective tissue. The work on achlorhydria and hypochlorhydria in relation to rheumatoid arthritis has shown there is no significant relation which is also true of studies on "endocrine imbalance". Vitamin deficiency as a cause of rheumatoid arthritis has been shown to be without proof.

The pathology of rheumatoid arthritis is well established with early proliferation of the synovial villi and collections of cells, chiefly lymphocytes and histiocytes, in the deeper layers of the synovial membrane. Proliferation of the vascular endothelium is characteristic, with complete absence of the polymorphonuclear cells. Later a fibrinoid degeneration occurs which affects the collagenous connective-tissue bundles. The late stages of rheumatoid arthritis show a synovial membrane with lympho-adenoid nodules formed by perivascular collections of lymphocytes, histiocytes and plasma cells. (The appearance of these nod-

ules lends support to the tuberculous theory of origin of rheumatoid arthritis.) In still later stages the synovial membrane and villi become fibrotic with many of the blood-vessels blocked. This interference with nutrition causes the secondary osteo-arthritic changes. Radiologically there is loss of bone calcium through-out the skeleton which occurs before the cartilage destruction. Rheumatoid arthritis is characterized by a disturbance in the finer blood supply of the tissues chiefly capillaries, to such an extent that metabolic processes are interfered with. The central articular area of joint cartilage is without blood supply and hence is sensitive to nutritional disturbances on account of lack of compensatory processes.

Rheumatoid arthritis therapy is empirical. Sulphur therapy may be dispensed with to the advantage of the patient. Gold therapy appears to be a procedure generally accepted despite the occasional serious reactions of the gold. The chief toxic reaction being dermatitis. Vaccine therapy is losing popularity to gold therapy but is still used by many clinics. Focal infections should be treated on their own pathology and not with the idea of any miraculous cures of rheumatoid arthritis. Perhaps if Meyer's

work on "latent phlebitis" is definitely proved, focal infection will take on new significance. Exterogenic therapy has not been shown to be effective. Histamine will not cure arthritis but is a good adjunct to other forms of therapy. Inhaled carbon dioxide in relation to rheumatoid arthritis on the basis of muscle spasm and pain relationship to hyperventilation tetany is still being studied. Cobra venom injection had no effect on articular changes even when the pain is relieved. Physical therapy has a definite place in the treatment of rheumatoid arthritis and much of it consists of the application of heat in its various forms. The most important effect perhaps being the hyperemia, mobilization of immune bodies and sedation. Ultra-violet radiation is valued for its tonic features, infra-red light for its hyperemic effect. Hydrotherapy aids in strengthening the muscles, eliminates stiffness and acts as a general sedation. The electrical agent short wave diathermy has been disappointing for rheumatoid arthritis. Massive vitamin therapy is to be discouraged. Arthrotomy and lavage is a valuable means of treatment in carefully selected early cases.

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