As a blind person is unable to draw a portrait, so is a Vaidya in treating patients who does not have thorough knowledge of cannot treat the patient.
REVIEW OF THE MODERN LITERATURE

RHEUMATISM:

A general term for acute & chronic conditions characterised by inflammation of muscle and pain in its associated structures. It includes arthritis due to rheumatic fever or traumatic degenerative joint disease etc.

Although arthritis occurs in a number of different forms there are essentially two fundamental pathologic processes that affect the joints:

a) Inflammation which may be or a combination of each and

b) Degenerative changes which are primarily dependent on the limited capacity of articular cartilage to repair itself. The following classification of disease of the joints:

1. Arthritis due to specific infectious agents.
2. Arthritis of rheumatic fever.
3. Rheumatoid Arthritis
4. Degenerative joint disease
5. Arthritis due to gout
6. Neuropathic Arthritis
7. Traumatic Arthritis
8. Arthritis with blood disorders.

EVOLUTION OF RHEUMATOID ARTHRITIS:

If we trace the antiquity of rheumatoid arthritis an interesting picture emerges out of it. The disease arthritis as a whole or rheumatoid arthritis in particular is as old as civilization. The evidence of this disease has been found in the Egyptian mummies. But the nomenclature- “Rheumatoid Arthritis” has been carried only by Garrod in 1859. Since then this term has been gradually adopted throughout the world. However, Germans and French still prefer to call it as “Primary chronic poly arthritis” and “La poly arthritis chronouques evolutive” respectively.

In the Hippocratic writings the word arthritis appears but the clinical descriptions are given only of Podagra (gout) and of rheumatic fever. Aretus who
lived in the first century A.D. was the first man who has given a good account of a clinical condition resembling rheumatoid arthritis, describing the onset in smaller joints with spread to others along with systemic changes and deformities. He has also expressed that true cause of arthritis was only known to gods.

Only in 17th century Sydenham was able to differentiate acute and chronic rheumatism and further gout could be differentiated from chronic rheumatism by the end of that century. The definite relation of uric acid and gout was established in 1848 by Garrod. He also observed that high uric acid in blood is absent in rheumatoid arthritis. He could also differentiate osteo-arthritis from rheumatoid arthritis in the early part of the present century. There was another opinion “unless the observer be a slave of names, it must be allowed that it is not easy to call a case as one or pure rheumatoid arthritis” because most of the patients suffer in later stage. However, now there is no doubt that the types of changes in the above conditions are basically different, one is proliferative the other is atrophic.

Thus there is great role of Sir. A.B. Garrod in the evolution of rheumatoid arthritis as a disease entity. Earlier to his right from the hippocratic age to mediaeval period all types of joint lesions were considered under one heading arthritis acute or chronic. But the process of evolution did not after him as the difficulty of diagnosis of RA. was not solved. Because the etiology could not be discovered so no definite or positive proof for the diagnosis could be evolved. And the diagnosis of RA. was only done by exclusion method. To solve this difficulty American Rheumatism Association proposed criteria for its diagnosis in 1956 which was further validated for clinical use in 1958. They are as follows:

1) Morning stiffness.
2) Painful movement or tenderness in at least one joint (observed by Physicians)
3) Swelling of at least one joint (observed by Physicians)
4) Swelling of at least one other joint within 3 months of the first joint involvement (observed by Physicians)
5) Symmetrical joint swelling (observed by Physicians), with simultaneous involvement of the same joint on both sides of the body but excluding terminal phalangeal joint involvement.
6) Subcutaneous nodules (observed by Physicians) over bony prominence or external surfaces or in juxta articular regions.
7) X-ray changes typical of RA.
8) Positive test for rheumatoid factor (R.F.)
9) Poor mucin precipitate from synovial fluid.
10) Characteristic histological changes in synovial membrane
11) Characteristic histological changes in nodules.

**GRADATION OF DIAGNOSTIC CRITERIA:**
- Classical RA. fulfillment of 7 or above criteria.
- Definite RA. fulfillment of 5 or 6 criteria.
- Probable RA- fulfilling 3 or 4 criteria.

But still the clinical diagnosis of rheumatoid arthritis is neither sure nor simple, because there is a group of disease as ankylosing spondylitis, Reiter’s syndrome, psoriatic arthritis and arthritis associated with chronic ulcerative colitis or regional enteritis which share a good deal of clinical and pathological findings with rheumatoid arthritis. These have been gradually identified and differentiated. The identification of rheumatoid factor in the serum and development of serological tests in last decade has greatly accelerated the above process. RF is found in the era of 70 to 80 % of patients with definite or classical rheumatoid arthritis. It can be detected in the blood by various techniques mostly involving agglutination reaction but common ones-are

i) Sheep cell agglutination test (S.C.A.T.)
ii) Bentonite flocculation test (B.F.T.) and
iii) Latex fixation test (L.F.T.) which have been extensively used in the study.

Now there is developing trend to classify the patients of RA. in two groups
i) Sero-negative and
ii) Sero-positive.

The prognosis of the two groups is quite different Sero- positive cases have more sustained disease leading to greater disability in comparison to the
other. It has been observed that mostly patients of seronegative group are associated with other diseases as psoriasis, ulcerative colitis and rheumatoid spondylitis and many in this group are associated with those in whom the arthritis develops at a younger age. Not only this the patients of sero-negative group should be seperated in all the studies and clinical trials because today one is not sure that sero-positive and negative cases are having the same disease or different. Thus we find that we are just on the border of further evolution ie. to seperate the seronegative cases from RA. and this process of evolution has to go on further till the aetiology of this disease is not confirmed.

In short one can sum up the process of evolution regarding the disease entity of RA. in modern medicine that in the early days all types of arthritis were grouped together under one heading and following the path of gradual evolution so many types of lesions have been recognized, differentiated and many specific types of arthritis have been recognized both of infective and metabolic origin. In the last few decades, the process of evolution has been separated from the same. In the phase of evolution the current problem is to differentiate the seronegative and sero-positive cases, of course the process is not complete and such developments are bound to occur till the aetiology of RA. is known.

RHEUMATOID ARTHRITIS:

In the early medical literature, there are several references related to Rheumatoid Arthritis, Hippocrates recognised the disease in early time. Thomas Sydenham described a disease first which he called as “Rheumatoid Polyarthritis”, the first differetiation of disease is usually attributed to Landre-Beauvais (1800) who published his observation as a thesis and described the clinical feature under the heading of “Goute asthenique premitive”. Earlier sayvager ((1763), Heberden and Musgrave have described the clinical features of the disease but without clearly identifying it as a separate disease entity.

In 1859 Garrod used the term Rheumatoid arthritis and clinical description of the disease entity began to emerge. He also noted that elevation of blood uric acid levels was not found in rheumatoid arthritis. The term rheumatoid arthritis has become widely adopted all over the world.
Cornil in 1864 first described Juvenile Rheumatoid Arthritis. Later in the 1897 Skills classical paper on juvenile arthritis appeared. This description was a landmark of straight forward clinical analysis and documentation and since it was original publication, has provided us with an amazingly preceptive analysis of the disease in children. In 1898 Bannatyne described bacterial etiology. The theory of focal sepsis was introduced by William Hunter (1901) and further popularised by Sir William Willcox (1935). Auto immunity subsequently held the field.

The arbitrary clinical differences between rheumatoid arthritis and degenerative arthritis was clarified in 1909 by an excellent monograph by Nichots and Tichardsen which clearly differentiated between proliferative and degenerative arthritis on the basis of pathological lesions.

There was little progress in development of the concept of rheumatoid arthritis as a generalised systemic disease until the early 1930's when Millard Smithes observation reaffirmed the original idea outlined by Still, Jonnes and Bannatyne. The reports by Cletcher and Lewis Faming were among the earlier large series in which particular attention was directed at radiographic aspects of the disease (1950). In 1957 Short, Bauer and Reynolds published the comprehensive survey and analysis of the problem. This book set the stage for the modern era of investigation and inquiry in the field of clinical rheumatology.

With a careful drafted description of the disease available and the later evolution and implementation of American Rheumatism Association Diagnostic Criteria for rheumatoid arthritis, the time came for more detailed analysis of the pathological process itself. From 1957 to the present, some of the most exciting advances related to the rheumatoid arthritis occurred in the areas of pathology and immunology.

AETIOLOGY:

The exact aetiology of rheumatoid arthritis is not yet known, various features like infection, biochemical, immunological changes and familial predisposition etc, which either proceed or are associated with rheumatoid arthritis have been extensively studied.

The aetiology of rheumatoid arthritis has been an everchanging concept in modern medicine. Neuropathy, vascular phenomenon, infection, endocrine disturbance,
altered immune response, metabolic disorder etc. have been considered as causative factors from time to time. In addition, because of having diverse clinical and laboratory findings in rheumatoid arthritis, speculations are done that either these expressions may be due to variable host responses against a specific cause of rheumatoid arthritis which may be discovered in future or the joint inflammation in this disease may be considered to be not the result of any specific initiating agent but rather that the rheumatoid patient provides as unique milieu in which any capable of producing joint inflammation could set into motion a self-perpetuating series of events. Thus there is suggestion of multi causal theory in the aetiology of rheumatoid arthritis.

In the last century, on the basis of neurological symptoms e.g. muscle weakness, tremors, radiating pain, hyperactive tendon reflexes and atrophy of muscles, it was thought to be a neurogenic disease. It is further suggested by symmetrical distribution of lesions. Cellular changes in anterior horn cells of spinal cord were described in the past but subsequent studies failed to show any specific central nervous lesion.

VASCULAR THEORY:

The theory of vascular origin of this disease is based on clinical findings of increased vasomotor tone, diminution of blood supply to extremities and lowered capillary resistance in the patients of rheumatoid arthritis. Further the pathological lesion in small peripheral vessels have also been demonstrated as vasculitis, venulitis and their complete obliteration. But the opinion is divided, whether these changes arise after the onset of articular symptoms or precede the onset. These changes in the vessels are explained as a part of the diffuse connective tissue change.

In addition to the arteritis and thrombosis the patients of rheumatoid arthritis having peripheral neuritis invariably have shown to have necrotizing arteritis. To demonstrate such lesions it is better to take the muscle biopsy from the area of neurologic deficit.

These lesions are similar to those found in polyarteritis nodosa, of course, they tend to involve smaller arteries than in the latter. It has been suggested that
these lesions may be due to corticosteroid therapy as they have been frequently demonstrated in era of cortisone but evidences are not in favour that cortisone plays role in the pathogenesis of necrotising arteritis.

However, it may be concluded that though the vascular lesions form important pathological features of rheumatoid arthritis, it is difficult to deside whether these indicate a susceptible soil or these are only the result of this disease.

**INFECTION THEORY:**

With the advent of germ theory of disease the other concepts of casuation gradually lost sight, in search for a microorganism which caused this disease. Variety of organisms were isolated from the rheumatoid body fluids and tissues and have been claimed to be specific causative agents in the past, but in due course of time failed to establish their specificity. Considering this disease to be due to virus, repeated attempts were done, to isolate viruses, but they were also a failure. Later on interest of the workers aroused regarding Pleuro - Pneumonia Like Organisms (PPLO). The usual characteristic of this organism is that unlike bacteria it lacks cell wall and like viruses it can grow on lifeless medium. Another interesting point with this organism is its prevalence in the spontaneous arthritis of animals. But the isolation of PPLO have not been confirmed from the tissue of the rheumatoid arthritis patients.

In the recent past focal theory of infection was also examined closely. It has a clinical support as it is observed that there is improvement in the joint lesion along with the improvement in the general condition after the eradication of the foci in rheumatoid arthritis patients. But it can not alter the course of the disease hence it can not be considered as a primary- cause.

It has been suggested that this may be the result of a combination of metastatic infection and tissue hypersensitivity. The tissues are sensitised by repeated minor infections, or a chronic infective focus discharging periodically bacteria in the blood and finally a bacteraemic episode results in disease. This view is further supported by experimental models, i.e. the rabbit joints are sensitized
by repeated infection of streptococci. But this suggestion does not explain that why a vast majority of people with infective foci do not develop the disease.

Thus, though at present the relation of micro-organisms could not be substantiated in the aetiology of rheumatoid arthritis, yet many workers are still hopeful to find some infection as the causative factor.

ALTED IMMUNE RESPONSE:

On finding no infectious agent as the causative factor, the best available approach to explain the mechanism of inflammation in rheumatoid arthritis is the altered immune reaction. Detailed studies have been done regarding immunologic mechanism causing inflammation in the recent past. Vascular changes, gamma globulinaemia, lymphoid proliferation are some of the glaring points catching the attention towards this theory. On this basis majority of workers in the field of rheumatology have agreed at present to consider the altered immune response as, primary pathogenic mechanism in the causation of rheumatoid arthritis. The advantage of this theory above others is that it is able to amalgamate all the prior proposals of aetiology and it has also been possible to put forth the experimental evidence in favour of this hypothesis. Linge could demonstrate the vascular and tissue changes in animals by injection of antigenically active proteins, similar to rheumatic diseases. Since then many experiments have been advanced in this field. It is evident that though the present stage of our knowledge needs perfection to explain the altered immune response theory but the points in favour are many and are found in majority.
HYPER SENSITIVITY IN RHEUMATOID ARTHRITIS

ANTIGEN - Lymphoid proliferation

FORMATION OF SPECIFIC-
SERUM FACTORS (ANTIBODIES)

ANTIGEN - ANTIBODY

REACTION

TISSUE CHANGES

VASCULITIS

GASTRO INTESTINAL AETIOLOGY OF RHEUMATOID ARTHRITIS

The co-existence of arthritis and disease of gastrointestinal tract has aroused increasing interest in recent years. On analysis the co-existence is found to be of two types. In one group, the gastro-intestinal changes follow the joint manifestations and the other these precede the arthritis. This observation contributes to the concept that the joint lesions are not only local changes but these are systemic disorders.

The example of the former are scleroderma, dermatomyositis, lupus erythematosus and polyarteritis nodosa. The nature of the collagen changes are similar in both the target organs, i.e., in the joints and gastro-intestinal arthopathies. The examples are arthritis associated with ulcerative colitis and regional enteritis.

Previously these lesions were considered as variants of rheumatoid arthritis but now these have been established to be separate clinical entities having quite different
etiopathogenesis and management. Recently few investigations have also started suggesting that the cause of rheumatoid arthritis, probably lies in the intestinal disorders. He opines that this intestinal lesion is caused by mal-adaptation to food specially the newer one that is wheat, rye and oat. These are supposed to produce enteropathy because of their protein complex, "Gluten" which is a noxious factor.

Epidemiological survey has proved the positive contribution of genetics in the aetiology of rheumatoid arthritis. Hence it has to be examined that how genetics operates upon the intestinal changes.

Coeliac disease is believed to be caused by the absence of Di-peptidase, an enzyme, which is an inborn error of metabolism. This change is also correlated with the intake of newer type of foods; with the growth of population the percentage of victims having hereditary entropathy is increasing. Shatin has advanced a hypothesis that these metro-zygotes comprise a genetic pool of subjects susceptible to rheumatoid arthritis. Of course, the precipitating factors may be additional having genetic or environmental nature. It is, therefore, not surprising to find that the highest incidence of rheumatoid arthritis is revealed in those regions where the population irrespective of race, subsides on wheat, rye and oats. On the other hand pathological studies of skeletons and mummies of new world among maize eating prehistoric American-Indians have failed to reveal evidence of rheumatoid arthritis where the staple diet was wheat and rye, from a long time.

However, the gluten induced trauma of the intestinal mucosa is not the only singular factor in causing absorption syndrome but entero-viruses, affecting the integrity of small intestine are equally important. With mal-absorption there is lowering of serum protein with relative increase of globulin which is frequently observed during the exacerbations of rheumatoid arthritis. The increase of γ-globulin may also be accounted due to genetic behaviour.

Thus briefly it may be concluded in words of Shatin "susceptibility to rheumatoid arthritis rests on one gene and two alleles. One recessive leading to enzymatic deficiency and the other linked with the first, a codominant allele controlling the production of polypeptide chains of gamma-globulins, the hypomorphic mutation of which leads to the production of the rheumatoid factor."
The hypothesis of malabsorption of aminoacids in the aetiology of rheumatoid arthritis is capable to explain the deficiency of protein, histine, arginine, glutamine and tyrosine and in turn the various lesions of the target organs may be easily explained on the basis of the deficiency of these essential amino acids (fig no. 3). Along with the protein deficiency, anaemia is another marked symptom of rheumatoid arthritis which is also explained by this hypothesis. Similarly low serum cholesterol observed in rheumatoid arthritis may be also due to improper absorption of the precursors necessary for the biosynthesis of cholesterol. Osteoporosis, a marked feature of rheumatoid arthritis is also found in association with coeliac disease.

ENTROPATHY AS PRIMARY CAUSE OF RHEUMATOID ARTHRITIS

ENVIRONMENT

1. DIET-INGESTION OF GLUTEN RICH DIET UNHYGIENIC DIETETICS

ENTEROPATHY

2. TRAUMA

3. STRESS etc. MALABSORPTION IMPEDED BIOSYNTHESIS OF PROTEINS IN SYSTEM EXCESSIVE DISSOLUTION OF COLLAGEN TISSUE

FIBRINOID CHANGES
COLLAGEN DISEASES
Eg. RHEUMATOID ARTHRITIS

Thus the clinical, bio-chemical and radiological findings found in rheumatoid arthritis all can be explained to be due to malabsorption. Epidemiological, genetic and immunological finding also support this view. Hence it may be considered as a primary cause. But the importance of this theory is only proved it. It has any practical value in the treatment, that is, with the prevention of enteropathy or by substituting the factors of mal-absorption the control of the disease should be made.

ENDOCRINE THEORY:

All the important endocrine glands, pituitary, thyroid and adrenals have been looked for, from time to time, to find out their role in the aetiology of rheumatoid arthritis. Low basal metabolic rate is a common finding in the patients of
rheumatoid arthritis. Susceptibility to this disease has also been observed in the women at the time of menopause. These findings could suggest the probability of involvement of endocrine glands in the disease. But the concept could get wide recognition after Hench and Kendall reported the beneficial effect of corticosteroids in its treatment. On this basis it was concluded that the disease might be caused due to deficiency of adrenocortical hormones. Having clinical proof this looked to be appealing but further investigations could not support its causal relation. The therapeutic action of ACTH can only be mediated through healthy adrenal glands, at the same time study on excretion of keto-steroids and 17 oxyhydrosteroid did not show uniform abnormality. Regarding the treatment aspect too, it is an established fact that steroids are capable to provide only a symptomatic relief so the possibility of its deficiency as causative factor is almost ruled out to-day.

In a low percentage of cases, thyroid deficiency has been also reported in the patients of rheumatoid arthritis and on that basis a thyro-hypo-physeal syndrome has been postulated but the percentage of this disorder is highly insignificant to denote its causal relation.

PATHOGENESIS OF RHEUMATOID ARTHRITIS

Though the aetiology of rheumatoid arthritis still remains unknown but attempt has been made to define the rheumatoid changes with the help of light and electron microscopic studies. The most characteristic lesion of this disease is demonstrated in subcutaneous nodules. The classical microscopic lesion of rheumatoid nodule consist of three zones.

1) Irregular central lesion of necrosis composed largely of amorphous eosinophilic debris admixed with some fibrin like material and remenants of collagen bundles
2) Surrounded by proliferating primitive fibroblast typically arranged in pallisade formation and
3) peripheral chronically inflammed connective tissue. This change is also termed as fibrinoid change. Basic change in this process is the dissolution
of the amorphous component of the collagen tissue which combines with the fibrous components, giving, swollen appearance to the tissue. This change is preceded by general inflammatory reaction with the predominance of vascular changes. Vasodilatation and increased vascular permeability with endothelial leakage represent prominent manifestation of the inflammatory response. Loss of fluid with resultant haemo concentration, increased viscosity and stasis is followed by exudation thrombosis, circulatory insufficiency and necrosis and cell death may result from failure to deliver metabolite to tissue as well as from insufficient clearance of toxic substances. These microcirculatory changes lead to gross tissue damage.

Among the vascular changes, venuitis is readily seen both in acute and chronic lesion but arteritis and arteriolitis are uncommon except in fulmination disease. Associated microscopic findings of the synovial membrane

i. marked vilus hypertrophy
ii. proliferation of superficial synovial cells often with pallisading
iii. marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells are predominating)
iv. deposition of compact fibrin either on the surface or interstitially.
v. foci of cell necrosis. Resultant gross features are congestion and

oedema of the synovial membrane giving it an appearance of redundantness which is fringy and pulpy in nature.

LYSOSOMES IN THE PATHOGENES IS OF RHEUMATOID ARTHRITIS

Role of lysosomes in the pathogenesis of rheumatoid arthritis is holding fast attention in the field of rheumatology. Lysosomes are minute intracellular structures better viewed by electron microscope. These are granular in nature having wide variety of hydrolytic enzymes taking part in digestive and lytic processes of cells. Inflammatory mediators capable of inducing increased vascular permeability,
chemotaxis and phagocytic activation have been identified. Normally these granules are surrounded by a membrane and the process of intracellular digestion is completed by a process similar to phagocytosis; avoiding the gross dissolution of the cell contents, while the period of fast active catabolism is associated, which may lead to auto digestion in autophagic vacuoles. Such vacuoles are formed by the cytoplasmic material including the lysosomal granules, which leads to active destruction. In addition rupture of the lysosomal membrane may take place directly and released enzymes may come in direct contact of whole cytoplasm resulting into its complete digestion. Release of enzymes from lysosomes may be inhibited by drugs and agents which tend to establish the lysosomal membrane e.g. aspirine, cortisone, gold salts etc.

Leucocyte lysosomes contain a substance, which is capable of increasing vascular permeability. Cathepsins released from leucocyte lysosomes have been shown to hydrolyse the protein, polysaccharide component of cartilage matrix. Thus the tissue changes, vascular changes and the changes in the cartilage matrix found in rheumatoid arthritis can be explained with increased lysosomal activity.

More recent studies have shown that intra-articular enzymes of lysosome are capable to produce acute and chronic changes in the joint. On these observations it has been hypothesised that an acute rheumatoid inflammation may be related to lysosomal enzyme activity and tissue breakdown. The relation of lysosomes with immune mechanism has also been suggested and it is observed that liberation of the lysosomes digested host tissue may act as antigen leading to the formation of autoantibodies which may be responsible for the chronic pathological changes. In short the lysosome theory is an interesting concept, may explain both the acute and chronic changes. At the same time the mode of action of the antiinflammatory drugs used for the treatment of this disease is also explained.
Chart: Pathogenesis of Rheumatoid Arthritis

- Trigger Mechanism
  - Genetic Susceptibility
  - Immune
    - Auto Immune Response
      - Synovial Inflammation
EVALUATION OF MODERN TREATMENT OF RHEUMATOID ARTHRITIS

Though there is no specific treatment known for rheumatoid arthritis because of its uncertain aetiology yet great achievement has been done in this field in the past few decades by finding out the suitable symptomatic of the disease. Success of the treatment depends upon proper selection of the disease and the clinical condition of the patient. The role of anti inflammatory agents is limited to stage one and two, which are characterized by soft tissue involvement and mild constitutional symptoms and are without any fibrous and bony changes. In the advanced cases reconstruction rehabilitation along with analgesics are the only suitable measure.

Infection as a aetiological factor has been studied by various workers like Bouchard (1891), Hunter (1901), Willcox (1956). Davidson in 1949, noted infectious foci in the patients of Rheumatoid arthritis. Similar observations were made in few patients by Empire rheumatic council in 1950.

Diphtheroids were isolated by J.J.R. Duthie et al (1967) from synovial membrane and fluid, but Bole at failed to isolate in patient with rheumatoid arthritis.

Bartholomew in 1956 isolated mycoplasmal group of organism from synovial fluid, serum, bone marrow and kidney in patients with rheumatoid arthritis but Bole 1973, Windoretal 1974 could not isolate mycoplasma in any patient of rheumatoid arthritis. Banetie et al 1966, Willcox 1973, attempted to isolate viruses from synovial fluid & membrane. Neither virus from the culture nor significant antiviral antibodies in the sera was found in the patients with rheumatoid arthritis.

Autoimmunity was thought to be responsible aetiological factor due to following reasons:-

1) Creation and explanation of experimental models for joint disease of rheumatoid arthritis required knowledge on immunological basis (Ziff 1965).

2) Cochrane (1967) showed that the rheumatoid factor and circulatory antibodies to the tissues and cells found in the patients of rheumatoid arthritis are also present in other connective tissue disease.
3) Vaughan et al (1966) demonstrated the key role of localisation of antigen antibody complexes in the blood vessels of patients with rheumatoid arthritis.

4) All these points were interpreted in the light of failure to isolate contently any single infectious agent.

Parker et al (1952) demonstrated in vitro and also in the sinovial fluid the formation of immune complexes between rheumatoid factor and gamma globulin. By immunofluorescent technique Hamerman (1968) and Fish et al (1966) reported localisation of various classes of gamma globulin. R.A. factor and complement in synovial membrane of rheumatoid arthritis. Britton et al (1971) demonstrated the presence of IgG-IgG complex, IgM( R.A.factor) and complement in leucocytes of synovia.

Psychological factor were also thought to be one of the aetiological factor because of closed temporal relationship between the periods of anxiety and the exacerbation of the disease. Cobb et al (1939) found emotional stress as a precipitating factor.

Trauma as a precipitating factor was reported by Kelly, Chhetri et al (1939) Chhetri et al (1970), and Vaishnava et al (1970) found emotional stress as a precipitating factor.

Vaishnava et al (1970), Jacoby (1973). Surgical procedures as a pricipitating factor was reported by Chhetri et al and Jacoby et al.

Hench (1934) reported effect of pregnancy over rheumatoid arthritis in the form of remission in the symptoms during the pregnancy. Empire rheumatic council reported improvement in the symptoms of rheumatoid arthritis in some patients, while deterioration after parturition. While Chetri et al (1969), Jacoby (1973) reported pregnancy as a precipitating factor.

AGE INCIDENCE

Disease can occur at any age. The Empire Rheumatic Council (1950) reported mean age 42 yrs. in males and 41 years in female. Male to female ratio was found to be 1:1.62. Short et al 1957 reported that the males over 15 years are equally
susceptible but in female marked increase in disease frequency occurs between 50 and 55 years, followed by decrease at 60 years and above. Miall et al (1958), Lawrence (1961) & Flemming et al (1976) found male to female incidence 1:1.8 and 1:1.1 respectively.

Indian authors found similar types & age and sex incidence, the ratio of male to female varies from 1:1.1 to 1:2.5 (Yadav et al, P.S. Shankar, Chhetri et al, Vaishnava et al.)

Peak incidence of disease found to be on lower side than that of Western authors.

SEASONAL VARIATIONS:

Aggravation of symptoms of rheumatoid arthritis in winter season was noted by Empire Rheumatic Council (1950), Benette (1960), Lawrence (1960), Loxton (1959), Jacoby (1973, Flemming (1976), Vaishnava (1970).

PRODROMAL SYMPTOMS:

Empire Rheumatic council in 1950 first time has done a pioneering work upon prodromal symptoms which later on studied by various other workers (Kanyerezi) et al (1960), Chetti et al (1970), Vaishanava et al (1970). These are loss of weight, nervousness, morning stiffness, fatigue and fever etc.

ONSET OF RHEUMATOID ARTHRITIS :-

Depending upon the mode of onset of rheumatoid arthritis it is grouped under sudden, or acute, subacute or intermediate, slow or insidious. This classification was introduced by Fleming et al (1976).

SUMMARY AND FREQUENCY OF JOINT INVOLVEMENT

Bilaterally symmetrical joint involvement was found by many authors viz. Dubey et al 1964, Vainshana et al (1970) Kanyerisi et al (1970), Fleming et al (1970). Though in majority of patients the joint involvement was bilaterally symmetrical, it was not so in all the cases (Ragen et al (1962).
Frequency of individual joint involvement was also studied by various workers Jacoby et al (1973), Greenwood (1969), Chhetri et al (1969), P.S. Shankar (1969), Vaishanava et al (1970). Their percentage of frequency of individual joint involvement varies, but bigger joint involvement was found more in all above series.

Pain and swelling of joints was reported by Vaishanava et al (1970), Greenwood (1969) and Dubey et al (1964). The swelling is due to the synovial thickening, proliferation of synovial tissue and increased volume of synovial fluid (Copeman 1970).

**DEFORMITY:**

Deformity in the joints results from destruction of articular cartilage, weakening of ligaments, tendons, capsule, muscular imbalance and physical force associated with the use of affected joints. Gerald in 1973 described following types of joint deformities.

1) **Ulnar deviation of fingers** which results from subluxation of metacarpophalangeal joints and enlargement of proximal interphalangeal joints.

2) **Bautonniers deformity** :- Flexed proximal interphalangeal joint is forced through the extensor hood like button through the hole.

3) **Swan neck deformity** :- It is the contraction of intrinsic muscle of hand producing the hyperextension of proximal interphalanges and flexion of distal interphalangeal joint.

4) Hallux valgus

5) Fixed flexion deformity.

6) Nodular enlargement of flexor tendon sheaths giving rise to trigger flingure deformity.

Indian author reported different types of deformity, percentage of which varies from 20 to 60 percent (Chetri et al 1969), P.S. Shankar (1959), Vaishanava et al (1970).

**MUSCULAR ATROPHY**

Muscular Wasting is a constant finding & cannot be explained on the basis of disease (J.J.R. Duthie). In 1961 Steinberg and Wyhmpanny with the help of
electromyography, found the evidence of poliomyositis, but not correlated with the muscle biopsy.

Muscular atrophy was found ranging from 21 to 62, in Indian study (Chetri et al. 1969) Vaishanava et al. (1970). Flemming et al. reported wasting in small muscles of hand.

Tenosynovitis was reported by Vaishanava et al. 1970 in 37 percent cases of rheumatoid arthritis. Tendon on the dorsum of the hand and wrist were commonly involved than those of foot and ankle.

16) NON ARTICULAR MANIFESTATIONS:

In recent years much greater recognition has been given to the fact that rheumatoid arthritis is a generalised disease of connective tissue (J.I.R. Duthie). Many of the manifestations which in the past were regarded as complications, have been shown to arise from a common pathological lesion described as a fibrinoid necrosis involving the cells, fibres and ground substances of connective tissue. There may be little clinical evidence of the presence of these changes, out of a proportion of cases non-articular manifestations are prominent. These are divided into generalised and systemic.

A) Generalised Manifestation

Features like lymphadenopathy, rheumatic nodules, skin changes, vasculitis are included in general features.

It is significant that in 1896 Bhauffard et al first reported generalised involvement of the reticuloendothelial system and the lymphadenopathy with adult rheumatoid arthritis one year before. Still described his 12 cases in children. Short C.L. et al in 1957 reported that 36 % in literature and 29 % in his series showed lymphnode involvement. In the same series splenomegaly was found in 6.5 % cases. This type of relationship had been noted by others on several occasions (Me Crae, T. Micheli, F).

17) Indian authors also reported lymphadenopathy, percentage of which varies from 0.5 percent (P.S. Shankar) to 22.1 percent (Vaishanava).
Significant peripheral oedema was found by Fleming et al and Vaishanava et al, while localised oedema due to lymphatic involvement was reported by Kalliomaki et al (1968).

18) SUBCUTANEOUS NODULES

The subcutaneous nodules of rheumatoid arthritis is one of the most characteristic lesion of the disease. As usually seen in clinical practice, the extensor surface of the arm and elbow are the most commonly recognized sites. They may also frequently be observed on contact points on feet, knee, buttocks or scalp.

Vaishanava et al and Dubey et al maintained the presence of rheumatoid nodules in 2.8 to 10.5 percentage of cases. Mongan et al (1968) reported rheumatoid nodules commonly with seropositive patients than seronegative cases.

Presence of rheumatoid granuloma at unusual sites have also been found by Dumas L.W. etal, Noonan C.D. etal, Portner MM. etal, Ramirez R.J. et al, Rubin E.H. etal, Burrows K..G.O. & Yates D.A.H., Rheumatic granuloma that appears identical to rheumatic nodules may be present in aortic root, valve ring or myocardium producing functional lesions of valvular insufficiency on condition disturbances (Lebowit 1953). Presence of rheumatic nodules producing valvular insufficiency have been operatively removed and valves have been replaced successfully (lveson J.M.I.; Thandani, U.; Lonesow M et al).

Rheumatic nodules close to bone may often result in erosion of adjacent bone (Dorfman H. et al 1970). A recent report described formation of intraspinal / masses causing neural compression with dramatic clinical consequences (Friedman et al 1970 and Linqquist 1970).

Histologically subcutaneous nodules show central areas containing fibrin, varying amounts of mucopolysaccharide amorphous and cellular debris, collectively this material has been referred as fibrinoid. This is surrounded by large mononuclear cells (Macrophages) arranged in radially oriented rows or palisades. This is enveloped by outer zone of granular tissue containing lymphocytes and plasma cells. Sokoloff(1953) on the basis of exhaustive study
of very early rheumatoid subcutaneous nodules has presented persuasive

evidence that these lesions begin as area of necrosis of small arteries.

19) Rheumatoid vasculitis is the most dramatic and potentially fatal systemic

complication of rheumatoid arthritis. It is a large vessel vasculitis similar to polyarteritis

nodosan in its manifestations. It almost always occurs in patients with high levels of serum

rheumatoid factors (James William Hollingswerth and Ronald J. Saykal). The basis of

vasculitis would seen to be some sort of in view of immune precipitation, since

complement of immunoglobulin have been detected in the vasculitis lesions and serum


Many workers reported skin changes and vasculitis in rheumatoid arthritis but

Empire Rheumatism Council in 1950 documented the thing in the form of peripheral

vascular changes, sweaty hands and feet with cold finger. Sinclair in 1956 also reported

arthritis at autopsy. Similar type of findings were reported by Chhetre et al, Vaishanava

et al. Allison reported a chronic ulcer over leg.


palpable thyroid and salivary glands, but available evidence does not indicate

thyroid dysfunction influencing the disease (Copeman W.C.S.).

B) Systemic manifestation:

i) CARDIOVASCULAR SYSTEM:

Baggenstoss 1941, Sokoloff (1933), Lebouit (1963) Krik et al (1969),
Bonfico et al (1969) pointed out cardiovascular lesions in the form of apicocardial
fat involvement. The incidence varies from 30% to 60% An excellent recent
review of clinical picture of rheumatoid pericarditis was based on investigations
experience with 17 patients and analysis of 41 reported cases in literature (Franco
et al 1972). The triad of left sided chest pain, cardiomegaly and pleural effusion
disease in the form of regurgitation or stenosis of the valves, cardiomegaly,
congestive cardiac failure was detected by Sinclair et al (1956), Clark et al (1957),

ii) PULMONARY MANIFESTATIONS:

In 1957 Baker and Bywaters E.G.L., Copeman detected involvement of crico-aritenoid joint in rheumatoid arthritis with chief symptoms of hoarseness of voice, pain while coughing and swallowing and laryngeal stridor is due to involvement of recurrent laryngeal nerve as a result of arteritis of vasanervorum. Gresham and Kellawax (1958) reported a case in which extensive inflammatory infiltration of the larynx with destruction of cartilage led to death from respiratory obstruction. Pleural effusion in association with rheumatoid arthritis has been reported by Carr and Maynex Baggenstoss et al (1943), Aronoff et al (1955), Cruickshank (1957) and Vaishanava et al (1970). Flitman et al (1948), recorded pneumonitis. Caplan (1953) described unusual pneumonitis in the lungs of minor with rheumatoid arthritis which was later named as Caplan syndrome.

To describe rheumatoid lung lesions several classifications have been proposed and derived primarily from the basic types of lung disease observed. The four major clinical divisions are:

1. Chronic fibrosing pneumonia
2. Pleurasy with or without effusion.
3. Nodular lung disease
4. Diffuse intestinal fibrosis

iii) RETICULO-ENDOTHELIAL SYSTEM

Motulsky et al (1957), Coats et al (1931), found an impressive lymphadenopathy. In 1924 Felty A.R. demonstrated co-existence of splenomegaly, peripheral leucopenia with or without peripheral leg ulcers, this was later on termed as
Felty's syndrome. Chauffard et al (1896) first time recorded generalised involvement of reticuloendothelial system and lymphadenopathy with adult rheumatoid arthritis.

In 1932 the first splenectomy was done by Hanrahan E.M. Jr. and Millar S.R. for the treatment of Felty's syndrome. An initial dramatic improvement in leucopenia and arthritic symptoms of the patient was recorded (1935), but subsequently the death of this patient was reported about 18 months after surgery. Hatch F.N. (1941). Talkov et al (1942) after reviewing all the cases reported at the time observed that, the clinical case summaries of as many as 70% of the patients diagnosed as having Felty's syndrome did, indeed, demonstrate evidence suggesting that an accompanying disease (such as lymphoma, tuberculosis, subacute might be present. Hepatomegaly, if present with lymphadenopathy, is correlated with more pronounced granulocytopenia( Ruderman M. Miller and Pinals 1968)

iv) RENAL INVOLVEMENT

Early studies based on autopsy material was thought to be glomerular hypercellularity (Resenberg and Baggenstoss et al 1943). However work has not substantiated any clear cut glomerular lesion which may be considered a part of the rheumatoid process. Several studies based on renal biopsy findings have proved very informative (Pollak et al 1962. Berman et al 1962, Gibberd 1962). Lawson et al (1966) reported renal disease, papillary necrosis and death of patient due to renal failure.

Amyloidosis was detected as early as 1923 when congored test was introduced (Bennhold), but it's reaction with rheumatoid arthritis was shown 30 to 40 years ago (Ralph C, Williams Jr.). During last 25 years much difference of opinion has existed among many workers in this field as to dearrange whether or not derangement of immunoglobulins was fundamental to production and exantual deposition of amyloid. Indian authors have also reported similar types of renal changes.

V) CENTRAL NERVOUS SYSTEM

One of the most common sequela of rheumatoid arthritis may be compression or pressure on peripheral nerves adjacent to the area of inflammed sinovium. Most common area in which this is noted are median nerve at wrist, ulnar or posterior interossious at elbow and occasionally peroneal nerve near the knee. Clinical varieties

Tinel's sign is used to diagnose carpel tunnel syndrome. The ratio of male to female involvement in unilateral carpel tunnel syndrome is 1:2.5. But in bilateral involvement it is 1:9 (Garland et al 1963, Phalen 1966).

In the first definite series of patients (Heart et al 1957) showing neuropathy and rheumatoid disease, vascular lesions in blood vessels supplying the various peripheral nerves were described. Hart et al 1960 reported peripheral neuropathy in 42 patients of rheumatoid arthritis Beckett etal (1970) reported segmental demyelination but no arterial lesions. The report of apparent autonomic neuropathy in a group of patients with rheumatoid arthritis as measured by sweat response was significant (Bannett 1965).

Atlanto axial subluxation complicating rheumatoid arthritis appeared in 1951 in which death was shown to be due to medullary compression by the odontoid process which herniated through foramen magnum. Large series of case reports and reviews of this important clinical entity have appeared, Vignon et al 1955, Shart etal (1961) Laurie (1961), Martal (1963), Couton etal(1966), Robinson (1966),Mathews (1969), Park etal (1966). Rheumatoid discitis is the entity in which rheumatoid pannus arising directly in the middle of neurocentral joints may replace annulus fibrosis and normal intervertebral joints and normal intervertebral disc substance ((Blard 1967). Reported figures for incidence of AAS varies widely. Sharp et al 1961 reported 19percent of hospitalised patients while others reported it in 71 percent patients with severe rheumatoid arthritis and neck symptoms (Martel 1961), 25 % by Matthews.

vi) OUTER INVOLVEMENT :

It is manifested commonly as kerato- conjunctivitis sicca. Previously thought to be confined to those patients with other stigmata of Sjogrens syndrome. Eadie and Thompson 1955 -56 noted symptoms and signs of conjunctivitis associated with filamentary keratitis and reduction of lacrimal secretions, corneal
ulceration occurs in small proportion of cases Iridocyclitis has been noted with in slight impairment of vision but total blindness may result in more fulminant cases. Scleromalacia perforans due to rheumatoid nodule in sclera and band shaped opacity of cornea occur much less frequently. (P.S. Shankar 1969, Vaishanava et al.)

Non-granulomatous type of uveitis in 2.1 percent cases Acute involvement of eye in rheumatoid arthritis is probably episcleritis or seleritis (Lyne et al 1968). Corneal lesion known as "Contact lens" has recently been described (Lyne et al 1968). Hurd et al 1970 reported multiple choroidal nodule and retinal detachments thought to be due to many intra ocular rheumatoid granulomas. Wright et al in 1965 reported correlation between sacroiliac joint involvement in association with ulcerative colitis.

vii) GASTRO INTESTINAL LESION:

No specific gastrointestinal lesion seen. However, a few reports indicate some degree of malabsorption in patients with very little histologic evidence of atrophy of villous structures within the small bowels.
LABORATORY INVESTIGATIONS

Haemoglobin percentage and peripheral smear:

Various estimations of haemoglobin percentage was obtained by different authors. Freireich et al (1957) reported lower mean haemoglobin concentration 11.7 gm% in 42 cases, as compared to 10 controls i.e. 14.9 gm%. Corbel] et al (1967) reported 13.5gm% in 19 percent of patients. Vaishanava et al (1970) pointed out Haemoglobin level as: below 5 gm% in 2.8 percent cases, above 10 gm% in 38 percent cases, and between 5 to 10 gm% in 58.4 percent cases.

Peripheral smear pictures were of different types.

1) Normochromic normocytic
2) Normocytic hypochromic
3) Microcytic hypochromic
4) Megaloblastic
5) Diamorphic

Patridge et al (1963) demonstrated megaloblastic anaemia (1-38 %). Chhetri et al (1969) hypochromic anaemia (41%). P.S.Shan kar pointed out normocytic hypochromic anaemia (21.9 %). Vaishanava et al demonstrated normocytic normochromic (40.4%), normocytic hypochromic (24.4%), microcytic hypochromic (22.1%), diamorphic picture (10.1%). Hence no specific type of anaemia could be correlated with the disease.

White Blood Cells:

Counts are usually within normal limits but moderate leucocytosis can occur with active disease process, pleurasy or pericarditis. Cchethri et al noted leucocytosis in maximum number of patients. P.S. Shankar demonstrated leucopenia. Vaishanava et al. pointed out leucocyte count as within normal limits. To et al signified mean W.B.C. count as 7900/- cmm Mean neutrophil count was varying from 5200/- cmm. Carthison et al demonstrated thrombocytosis.

ERYTHROCYTE SEDIMENTATION RATE
It is an accurate index for detecting the disease activity in follow up cases. Raised ESR values were signified by Empire Rheumatic council, Dube et al Chhetri et al. Carbett et al P.S. Shankar, Vaishanava et al etc.

RECENT CONSIDERATIONS IN RHEUMATOID ARTHRITIS

1) Role of genetic influences in the etiology of RA was established by the demonstration of an association with the class-II major histocompatability couples genes products, HLA-DR-4.

2) The haplotype HLA-DR-4, appears to be associated with more severe manifestation of RA including Felty's syndrome, whereas pulmonary involvement in RA is associated with HLA-DR-4.

3) Genes controlling the expression of the antigen receptor on T cells have also been associated with the development of RA.

4) Genetic risk factor cannot fully account for incidence of RA, suggesting environmental factors also play role in the aetiology of the disease.

5) The predominant infiltrating cell is the T-lymphocyte. T₄ cells predominate over T₈ cells and are frequently found in close proximity to HLA-DR macrophages and dendritic cells. T₈ cells are largely of cytotoxic nature.

6) Analysis of T₈ cells in synovial fluids has documented on enrichment in CD 29-expressing memory T₄ cells and a marked reduction in the number of CD-45R expressing Naive T₄ cells.

7) The infiltrating T cell appear to be activated, since they expressed an increased density of molecule and activation antigen such as HLA-DR. Finally the T cell appear to have proliferated in the synovial tissue.

8) B-cell activation can also be found in the inflammed synovium.

9) The persistent inflammation could result from deranged immunoregulatory mechanism that are either primary abnormality or develop as a result of local inflammatory response.

10) The precise mechanism by which bone and cartilage destruction occurs has not been completely resolved. Although the synovial fluid contains a number of
enzymes potentially able to degrade cartilage.

RADIOLOGICAL FEATURES:

Various types of radiological changes are observed

1) Radiologically normal cases
2) Juxta articular osteoporosis
3) Soft tissue swelling
4) Marginal erosions of articular bones
5) Surface erosion of articular bones
6) Apparent narrowing of joint spaces.
7) Real narrowing of joint spaces
8) Deformity of articulation
9) Subluxation and dislocation.
10) Bony ankylosis.

Lewis (1955) stated that, “Diagnosis of early rheumatoid arthritis, study of the hands is particularly regarding.” Long before cartilage or bone destruction occurs there are three areas of soft tissue swelling which may announce the presence of the disease.

1) Fusiform soft tissue swelling of bone of several proximal interphalangeal joints.

2) Capsular distension of one or more metacarpophalangeal joints.

3) Localised soft tissue swelling on the ulnar side of the wrist, about or just distal to the lower extremity of the joint of ulna.

Reversal of albumin & globulin ratio was demonstrated by Dubey (1964) and Asha Mehta. Serum uric acid level was raised in 1 percent cases as per E.R.C. (1950), Greenwood Toha.