DAPSONE IN RHEUMATOID ARTHRITIS

Thesis

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BY

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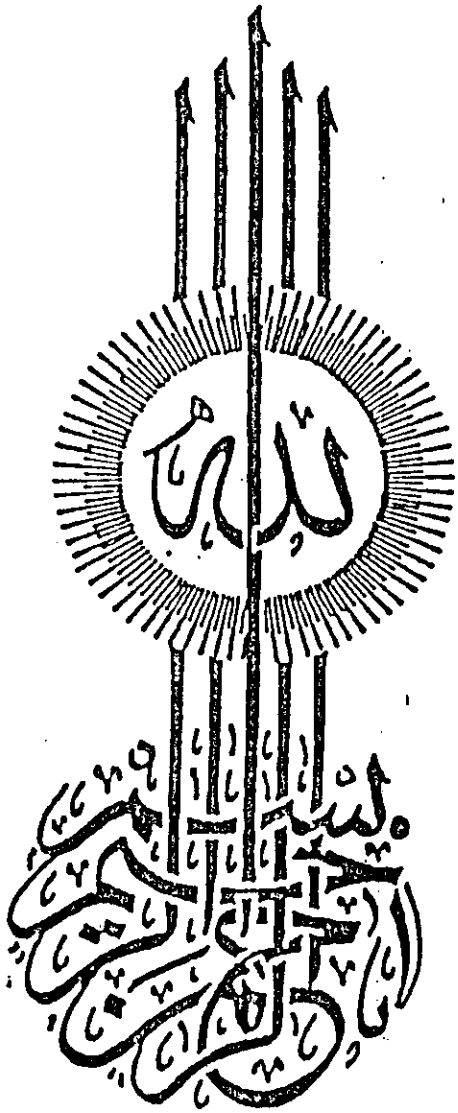

سبحانك

لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

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CONTENTS

INTRODUCTION

Dapsone is an antibacterial drug for leprosy, it is also effective in dermatitis herpeti-formis, a disease where the characteristic lesions are thought to be due to deposition of immune complexes (Seah et al., 1973). It therefore, seems possible that dapsone might have effects other than antibacterial, moreover some of the lesions of rheumatoid arthritis have been attributed to immune complex deposition (Glynn, 1972).

The magnitude of the effect of a drug on serum-C-reactive protein, erythrocyte sedimentation rate and the Rose-Waaler titre can be regarded as a measure of its efficacy, and the information provides a guide to how well the disease rather than just symptoms is controlled.

The aim of our work is to study the effect of Dapsone in the treatment of rheumatoid arthritis

Aetiology of Rheumatoid Arthritis :

Indeed, it is still not clear whether R.A. is one disease with multiple etiologies or a symptom complex produced by a single causative factor (Zvaifler, 1979).

Many thoeries have been proposed to explain the aetiology of rheumated arthritis.

1. Infection:

Over the past 50 years an extensive array of techniques has been used to isolate microbes or identify microbial particles in an attempt to prove that there is an infectious etiology for Rheumatoid arthritis, (Utsinger, et al., 1985).

No evidence currently exists, that rheumatoid arthritis is initiated by a streptococcal infection, interest then shifted to diphtheroids as etiologic agents when it appeared that they were present in synovial membranes and fluids, (Stewart, et al., 1969), but these organisms, which are part of the normal skin flora, were subsequently discredited as etiologic agents and are now believed to be contaminants, (Utsinger, et al., 1985).

More recently, claims have been made for the isolation of diphtheroid like organisms (Corynebacteria, now, called proprionibacteria) from rheumatoid synovium, (Phillips, 1982), and a polysaccharide antigen similar to that from

proprionibacterium acne has been demonstrated in phenol water extracts of synovial fluids and leukocytes, (Bartholomew and Bartholomew, 1979). Unfortunately, in both studies, similar organisms or antigens were Found in nonrheumatoid tissues in sufficent number to cause researchers to question. Their etiologic significance. (Utsinger et al., 1985).

From time to time, reports of mycoplasmas isolated from synovial fluid and membrane have appeared, but the majority of studies using a variety of sensitive detection methods fail to confirm them, (Person, et al., 1973).

There has been increasing interest in the possible role of Epstein Barr virus (EBV), a herpes virus, based on a high prevalence in rheumatoid arthritis sera of antibody to nuclear antigen (RANA) present in EBV-transformed lymphoblastoid cell lines (LCL), (Tan, 1979). Patients with rheumatoid arthritis have defective immune regulation of EBV-infected lymphocytes, and this defect may explain the differences reported in the expressions of antibody to EBV antigens in these patients, (Utsinger et al., 1985).

Persistent synovitis with hepatitis (B) arthritis has been well documented (Duffy, et al., 1976).

Entrovirus antibodies were not found, (Hart, et al., 1979). In general, antibody studies have failed to support for

a viral infection in rheumatoid arthritis, (Currey, 1978).

2. Autoimmune mechanism:

Rheumatoid arthritis, now is regarded as an autoimmune disease implying that the central fault is an abnormal immune reaction directed against some body components. (Bennett, 1981).

The evidence for an immunologic mechanism includes :-

- Histologically the synovial tissues in RA show vast accumulation of cells of the immune system including small lymphocytes and plasma cells which are aggregated into lymphoid follicles. These cells are producing, amongst other things, antibodies to IgG which must have been altered in some way so that it is rendered antigenic to the immune surveillance systems. These autoantibodies are rheumatoid factors and are found in all classes of immunoglobulin, but predominantly in IgM and IgG. (Dieppe, et al., 1985).

- Zvaifler (1974) has found good evidence that rheumatoid synovitis is associated with the presence of immune complexes in the joints. Currey (1978) stated that such complexes might form in one of three ways:

1. Combination of rheumatoid factor with free immunoglobulin G.

2. Combination of rheumatoid factor with immunoglobulin G already bound to an antigen, whether this antigen be a normal or altered joint constituent, a product of

inflammation, or an infective agent.

3. Self-association of immunoglobulin G-rheumatoid factor (IgG-RF.).

These complexes activate the complement system and thus cause polymorphnuclear leucocytes to migrate into the joint. These cells phagocytose the immunocomplexes and in so doing, release lysosomal enzymes which act as chemical mediators of inflammation and are the immediate cause of synovitis, (Zvaifler 1974).

- Reduced complement activity in synovial fluids from active rheumatoid joints and lowered serum complement leveles in patients with active systemic disease (Hunder and McDuffie, 1973).

- Cell-mediated immunity is abnormal: skin reactivity to antigens such as tuberculin is depressed in active RA; draining, the thoracic duct removes T lymphocytes and ameliorates RA and re-infusing them results in a flare of disease. Total lymphoid irradiation is also often successful in suppressing disease activity.

- Cytotoxic drugs can be used to induce disease remission and these agents have a profound effect on the immune system (Dieppe, et al., 1985).

3. Genetic factors:

Family and mono-and dizygotic twins studies have shown that there is a weak genetic factor in RA, (Panay, 1986).

In RA the important observation was the finding that HLA-D_4 and HLA-DR_4 are significantly elevated in RA, being found in 60-80% of patients compared to 20% of control subjects (stastny, 1978).

Family studies confirm the association of DR^4 with RA in caucasians but have shed no additional light on further genetic factors or on the exact location of the RA disease susceptibility gene within the MHC. Clearly genes at other loci and even on other chromosomes may be involved since some immunoglobulin Gm haplotypes are found more frequently in sibling pairs than would be expected by chance (Zilko , et al., 1980).

The concensus of current research is that HLA-DR_4 is not a marker for the propensity to develop rheumatoid factors either in normals or in patients with RA (Panayi and David, 1983).

There is evidence that HLA-DR_4 may be a marker for an immune response gene to denatured collagen in that DR_4-positive individuals, whether healthy controls or patients with RA, are able to mount, a 'T' lymphocyte response to this antigen wheras DR_4-negative individuals fail to do so (Smollen et al., 1980) and Solinger, et al., 1981). The unresponsiveness of DR_4 negative individuals may be due to the presence of circulating suppressor 'T' lymphocytes able

to switch off this response (Solinger and Stobo, 1982).

Nevertheless, despite these findings there must be other factors involved in the susceptibility to developing RA since only a small proportion of DR_4 positive individuals in the community have the disease. It may be that following joint damage initiated by other means, cell-mediated immunity to collagen in DR_4-positive patients would accentuate tissue destruction by secondary auto-immune reactivity. This leads to the concept that DR_4 is a marker for disease severity rathar than disease susceptibility (Panayi, 1986).

Recent reports suggest that patients response to specific forms of Therapy may be related to an individual's genetic make-up such as the observation that patients with rheumatoid arthritis manifesting toxic responses to chrysotherapy exhibit a significant increase in the HLA-DR_3 phenotype (Coblyn et al., 1981). However, there is evidence that the possession of DR_2 is associated with milder disease and with a better response to second-line drug treatment-especially sodium aurothiomalate (Panayi, et al., 1978).

The PATHOGENESIS of Rheumatoid Arthritis:

According to panayi (1986) rheumatoid arthritis was described as:

1. A disease caused by an environmental agent, which evades

the host immune system as a result of genetically determined immunodeficiency on the part of the host.

2. The entry of lymphocytes into the joint by means of specific recognition structures on lymphocytes and on high venular endothelium through which cells migration takes place.

3. Persistence of the agent and/or failure of immune regulation leading to immune hyper-reactivity including, the generation of RFs and immune complexes.

4. The release of a variety of mediators with effects on lymphocytes, macrophages, osteoclasts, vascular endothelium and chondrocytes.

The hypertrophic and hyperplastic rheumatoid synovial membrane is infiltrated with chornic inflammatory cells such as macrophages, T and B lymphocytes and plasma cells. Some 70% of the latter are producing IgG and IgM rheumatoid factors, but the nature of the immunoglobulin produced by the remainder is not known. Immune complexes are present in abundance both extra-cellular and intra-cellular either as phagocytosed material or as self-associated IgG rheumatoid factors within plasma cells (Munthe, 1978).

There is also increase in the number of blood vessels in the inflammed synovial membrane and this could be due to the production of angiogenesis-promoting factors or to loss

of angiogenesis-inhibiting factors normally made by articular chondrocytes. (Panayi, 1986).

The perivascular lymphoid aggregates in the rheumatoid synovium are predominantly localised around areas of high venular endothelium (HVE) where Lymphocyte trafficking normally takes place as a consequence of specific lymphocyte-recognition-structures being present on HVE cells. Recent studies using histochemistry and immunohistology have shown that there are dendritic. interdigitating cells of a similar phenotype to antigen presenting cells in the "T" dependent areas of lymph nodes (HLA-DR-positive, lysosomal enzymes-negative, adenosine triphosphatase-positive) scattered throughout the synovial membrane (both normal and inflammed) but particularly in a perivascular distribution. In the rheumatoid synovium these cells are intimately associated with "T" lymphocytes of a helper/inducer phenotype (OKT_4-positive). These cells are the majority "T" cell population except at the periphery of the perivascular aggregates, where "T" lymphocytes of the suppressor/cytotoxic phanotype (OKT_4-positive) may, on occasions, predominate and in small lymphocyte collections scattered in the synovium where the ratio of T_4 and T_8 lymphocytes is close to unity (Duke et al., 1982), and Poulter et al., 1983).

This arragement is particularly suited for lymphocyte activation and the generation of a wide variety of interleukins, lymphokines and other inflammatory mediators. Thus the activation of T_4 helper lymphocytes would lead to "B" cell activation and differentiation into plasma cells producing Rf and other immunoglobulins, it should be noted. However, that on this view the predominant immunopathological event in the RA synovium is a T-dependent one (Janossy et al.,1981).

Some of the factors released in the inflamed synovium could have a variety of effects. Thus activated macrophages could release interleukin 1 (IL 1) which could have local as well as systemic effects, systemic effects would in particular, include, the stimulation of the acute phase response including elevation of C-reactive protien. T_4-positive helper/inducer lymphocytes produce interleukin 2 which then activate other "T" cells to proliferate, others to make interleukin 3 capable of activation macrophages, and yet others to produce "B" cell activating and differentiating factors with the ultimate generation of immunoglobulin producing plasma cells. The activation of macrophages or of large stellate synovial cells by IL 1 (mononuclear cell factor) leads to production of collagenase and prostaglandins with obvious tissue degradative and

inflammatory potential (Baum,1982).

Persistent disease would then be the result of the persistence of antigen (RA agent) and/or inadequate "T" lymphocyte suppression so that a chronic, self-perpetuating inflammatory system could be set up. There is even the possibility that after the initial trigger by exogenous antigen the whole process could become auto-stimulatory as in the autologous mixed lymphocyte reaction (Janossy et al..1981). if so, rheumatoid arthritis would be the first of a new type of autoimmune disease whose persistence depends on the failure to switch off autoreactivity to the DR products of the major histocompatibility complex (Panayi, 1986).

Pathology of Rheumatoid Arthritis :

Pathology of arthritis is described by considering the following :

1) Synovial pathology :

The synovitis of RA affects all joints, tendons and bursae that have a synovial lining. The earliest changes seen in the synovium are vascular congestion and oedema followed by a marked increase in the numbers of synovial lining cells and fibroblasts, infiltration of cells from circulation mainly T lymphocytes and plasma cells, and tissue macrophages derived from circulating monocytes. The lymphocytes and plasma cells aggregate to form recognisable lymphoid follicles (Dieppe et al.,1985).

From the earliest moment in R.A.synovitis, altered venular permeability allows plasma proteins to pass into the extravascular tissue spaces where, they can be identified in the oedematous fluid. This proteinaecous exudate tends to be reabsorped into synovial lymphatics but some is removed by phagocytes. IgG, IgM and IgA immunoglobulins, together with complement, take part in local antigen-antibody reactions (Clemmensen et al.,1983). Fibrinogen represents only a small fraction of the total exudate but readily polymerises in the extracellular spaces. The resultant accumulation of insoluble fibrin. Although much fibrin remains within the

subsynoviocytic tissue. a large part of the initial exudate escapes through the readily permeable synovial cell layer into the joint space (Holland, et al., 1982). Here, the quantity of polymerised fibrin may be so large that it aggregates into melon-seed-shaped structures, often called 'rice bodies' (Popert, et al., 1982). Occasionally, and in a small proportion of cases, microscopy reveals foci of necrotic material within the subsynovicoytic connective tissue. True intra-articular granulomate have been described (Kampner and Kuzell, 1976).

As the disease becomes established and progresses, the overgrowth of cellular elements causes even more thickening of the synovium and a marked increase in surface area, producing great seaweed_like fronds, hence the name villous synovitis. The macrophages in this inflammatory granulation tissue or pannus produce destructive proteases and collagenases (Dieppe et al., 1985).

Electron microscopy of synovial membrane shows enlargement of type "A" lining cells, small Golgi apparatus, abnormal mitochondria, large vacuoles, enlarged and ruptured lysosomes, and many dense granules (residual bodies) which show acid phosphatase activity and certain remnants of phagocytosed material incompletely digested by lysosomal enzymes. These changes suggest altered metabolic activity of

the synovial lining cells (Golding, 1982).

Within a few days of the onset of rheumatoid synovitis, reparative processes of granulation tissue formation and fibrosis are evident (Gardner, 1986).

Active disease, assessed microscopically, often persists when the clinical state is quiescent. The synovium becomes dull-red, granular and less swollen. Cartilage destruction and the extension of pannus are accompanied by the formation of new fibrous tissue which links and then binds together the peripheral margins (Gardner, 1986).

2) Cartilage destruction:

The natural History of R.A. is dominated by the inexorable destruction of hyaline cartilage, cartilage destruction imparis movement and load-bearing and leads to inefficient lubrication. The replacement of the avascular cartilage by the vascular granulation tissue of the pannus further impedes movement and provokes fibrous ankylosis (Gardner, 1986).

The first microscopic sign of cartilage degradation are recognised at the periphery of the articular surfaces, in the junctional zone where synovium adjoins cartilage at this site. There is diminished fibronectin (Shiozawa and Ziff, 1983).

The inflammattory exudation in the joint cavity,

especially the fibrinous exudation increases the viscosity of the joint fluid. Therefore, the diffusion capacity decreases which impedes the supply of metabolites necessary for the survival and synthetic mechanisms of the normally avascular cartilage (Uchlinger, 1971).

Dingle, et al., (1974) have claimed that one enzyme system (e.g. of cathepsins) may affect early depolymerization of matrix proteoglycan, removing a component essential for collagen fibres integrity, allowing a second system (of collagenases) to destory collagen and cause irreversible structural damage.

A further local consequence of the increased regional blood flow that accompanies the synovitis of R.A. is bone reabsorption. Local osteoporosis is, however, one factor contributing to the formation of the frequent peri-and subarticular pseudocysts. These are small, radiolucent foci lying beneath or near cartilage at sites of severe RA synovitis. The pseudocyst is a solid structure histologically: it comprises loose, vascular granulation tissue and is usually in continuity with marginal pannus (Gardner, 1986).

3) Juxta-articular connective tissues:

Bursae and tendon sheaths are common sites of R.A. synovitis. (Gardner, 1986).

The wall of the inflamed bursa is formed of dense collagen. There is a chronically inflamed synovium like lining, a variable lymphocytic and plasmacytic infiltrate, with few lymphoid follicles (Wagner and Abgarowicz, 1970).

A true tendinitis accompanies tendinous synovitis and the focal necrosis of tendon collagen that develops simulates the microscopic structure of R.A. granuloma. The rupture that follows may appear "spontaneous" and is occasionally bilateral. (Tarr, 1974).

4) Subcondral Bone:

Locally, bone is destroyed at articular matrgins by osteoclastic reabsorption, it is likely that , This response is calcitonin-dependent' but there are no known and consistent changes in parathyroid gland structure. The absence of reactive, new bone formation is unexplained. It is suspected that altered, increased blood flow may be an explanation for local bone destruction (Gardner, 1986).

The subchondral granulation tissue is contineous with that in the synovium, through defects in the cortex of the bone near the joints. Grossly, the marrow appears congested in these areas, The bone undergoes irregular osteolysis, (Sokoloff, 1974).

5) Anatomical consequences:

The key to the anatomical progression of RA is the

marginal centripetal, erosive synovitis. peripheral cartilage destruction in any joint with granulation tissue formation is recognised at arthroscopy or arthrotomy as a rim of pale-red exuberant material linked by bands of young fibrous tissue establishing adhesions that become denser and more numerous with time fibrous ankylosis is commonplace.

Bony ankylosis does not occur' its recognition suggests. the coincidence of another disorder such as bacterial infection or trauma.

Secondary phenomena such as amyloidosis, oesteoarthrosis. osteoporosis and fructure complicate. the initial polyarthritis, they are associated with the mechanical results of deformity and disease (Gardner. 1986).

The Clinical presentation and Course of Rheumatoid Arthritis

Rheumatoid arthritis, like so many other autoimmune diseases, predominantly affects females, in a ratio of 2-3 females to 1 male, (Buchanan and Kean, 1986).

Rheumatoid arthritis occurs in approximately 3 percent of adult population, (Golding, 1982). It may being at any time from the first few weeks of life until the ninth decade, but the peak time of presentation is 35-45 years. (Seifert, 1983).

Classically, the disease presents as a symmetrical polyarthritis occuring in the small joints of the hands and feet.

However, presentation as a monoarthropathy or in asymmetrical larger joints is well recognized and therefore, it is necessary to keep in mind the possible diagnosis of rheumatoid arthritis when faced with inflammatory arhtropathy (Seifert, 1983).

Patterns of Onset:

1. Insidious onset, rheumatoid arthritis usually has an insidious slow onset over weeks to months. 55 to 70 percent of cases begin this way (Fleming, 1976). The initial symptoms may be systemic or articular, in some patients

fatigue, malaise or diffuse musculoskeletal pain may be the first non-specific complaint. with joints involved later, morning stiffness may be the first symptom, noted even before pain. This phenomenon is probably related to accmulation of oedema fluid within inflammed tissues during sleep. morning stiffness disappears as oedema and products of inflammation are absorbed by lymphatics and venules and returned to the circulation by motion accompanying use of muscles (Harris, 1985).

2. Actue onset. 8 to 15 percent of patients have an acute onset of symptoms. The term "acute" refers to the rate of build up of symptoms. symptoms mount, with pain developing in other joints, often in a less symmetrical pattern than in patients who have an insidious type of onset. pain may be generated also by surrounding muscles, and muscle pain can be so severe as to mimic ischemic pain. (Harris, 1985).

3. Intermediate onest: 15 to 20 percent of patients have an intermediate type of onset, symptoms develop over days or weeks. systemic complaints are more noticeable than in the insidious type of onest (Harris, 1985).

Unusual patterns of onset of Disease:

1) adult onset still's disease. This disease appears in adults, usually in the third or fourth decade as a syndrome like that seen in children with the acute, febrile onset of juvenile arthritis (Baywaters. 1971). Fever patterns in these patients are usually quotidian (i.e. reaching normal levels at least once each day). patients have skin rash which become more prominent when patients are febrile. The arthritis usually involves fewer joints than R.A. in most adults. (Aptekar. et al.. 1973). Serology (rheumatoid factor and antinuclear antibody) is negative and patients have not developed subcutaneous nodules (Gupta and Mills. 1975).

2) Palindromic pattern of onset. The syndrome is more like gout than anything else. pain usually begins in one joint. symptoms worsen for several hours and are associated with swelling and erythema. An intercritical period as in gout, is asymtomatic. It is likely that 30 to 50 percent of patients with palindromic rheumatism develop R.A. in these. multiple joints become involved, swelling does not subside completely between attacks. and tests become positive for rheumatoid factor. Neither the characteristics of joint fluid nor the pathology of synovial biopsies allows the

prediction that palindromic rheumatism will develop into R.A. (Schumacher. 1982).

Course and prognosis:

The clinical course of the disease is very variable at least three main types can be distinguished.

1) In the first. the disease has an acute onset with wide-spread joint involvement and marked systemic upset, such patients often have a favourable prognosis.

2) In the second type. the disease starts insidiously with involvement of only a few joints and progresses with a steady deterioration in functional ability. but with little constitutional upset. although eventually the patient becomes severely crippled.

3) The third category. lies between these two extremes, the disease tending to run an irregular course of exacerbations and remissions. The eventual outcome of patients in this category is extremely varied (Buchanan and Kean. 1986).

Many associated physiological or pathological conditions may alter the course of disease e.g. pregnancy may be associated with spontaneous remission. however arthritis may flare after parturition.

Paralysis of limbs invariably decreases inflammation and proliferation of joints. This is to be contrasted with

the tremors of parkinson disease giving no rest from motion and accelerating joint destruction.

Obesity. incurs stress on weight bearing joints. Diabetes. which induces abnormal carbohydrate metabolism may interfere with proteoglycan metabolism in connective tissue. producing inadequate or altered matrix and enhancing the process of joint destruction (McGuire and Harris, 1979).

Although certain factors such as acute onset of short duration. initial asymmetrical and limited joint involvement. absence of joint effusions and erosions. and afavourable response to treatment appear to favour a better prognosis (Buchanan and Kean. 1986).

The most important single index is the titre of serum rheumatoid factor. patients with persistently high titres of rheumatoid factor have in general a poor prognosis. whereas those with low titres or intermittently weakly positive rheumatoid factor tests run a favourable course (Feigenbaum. et al., 1979).

Seronegative cases are thought to have a more favourable prognosis. which is unfavourable if seropositivity occurs within first year after onset (Golding. 1982).

Articular and Systemic Manifestations of Rheumatoid Arthritis

The manifestation of rheumatoid disease can be classified into two main group. articular and extraarticular lesions. However, the main brunt of the disease is borne by the diarthrodial joints, and the most rheumatologists still prefer to use the term "rheumatoid arthritis" (Buchanan and Kean. 1986).

I) Articular Features:

Any of the synovial joints of the body may be affected (Vernon-Roberts. 1975).

The clinical features of arthritis conform to the cardinal features of inflammation with one exception redness is never present. A red rheumatoid joint must always be suspected as being infected (Buchanan and Kean. 1986).

In rheumatoid arthritis pain perception is highly variable from individual to individual. There is an important interaction between depression and chronic pain each serving to exacerbate the other and this combination is common in early inflammatory arthritis (Dick and Goodacre. 1985).

Joint stiffness is especially troublesome in the morning. attributed to increased fluid content of the joint

tissues (Scott, 1960). Stiffness of the joints after sitting for some time-so called gelling is also very characteristic of rheumatoid arthritis (Buchanan and Kean, 1986).

As regarding the distribution of the joints affected it is extremely variable from patient to the other but the joints most frequently involved are the proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs, the meta carpophalangeal joints, the wrist, elbow and shoulder joints. The knee joints and the metatarsophalangeal joints in the feet (Jacoby et al., 1973). Involvement of the temperomandibular joint and the cervical spine are commonly present as early features in the disease presentation (Fleming et al., 1976).

1) Cervical spine:

Involvement of the cervical spine is extremely variable depending on the severity of the disease (Bland, 1974). As many as a third of patients have evidence of involvement on x-ray but the incidence of symptoms and neurological consequences is much lower.

Synovitis results in erosion of the odentoid peg and weakness and laxity of the transverse ligament (Dieppe et al., 1985)

Subluxation of the atlas on the axis is held in check by the alar ligaments subluxation may be either symmetrical

or asymmetrical. The lateral masses of the atlas and the occipital condyles may become eroded and collapse, with resulting basilar impression (Swinson et al., 1972).

With the odontoid peg-rising up into the foramen magnum-detected on lateral x-ray of the skull as encroachment of more than 4 mm. above McGregor's line (from the back of the hard palate to the inferior margin of the occipital curve) (Dieppe, et al., 1985).

Patients with atlanto-axial disease often complain of pain radiating along the distribution of the first and second cervical nerves, pain commences in the cervical spine and radiates upwards over the occiput and vertex to the forehead atlanto-axial dislocation may cause vertebrobasilar insufficiency or may produce neurological signs by direct pressure on the cord (Dick and Goodacre, 1985). Certain alarm symptoms include: severe pain, disturbed bladder function, decreased motor power, sensory changes and "Jumping legs" due to spinal automatism (Meijers et al., 1974). Death may occur as a result of spinal cord compression following atlanto-axial subluxation especially with neck manipulations e.g. during tooth extraction or intubation during general anaesthesia (Mathews, 1969).

Involvement below C_1-C_2 is relatively common both at the synovial apophyseal joints and the nonsynovial intervertebral discs and may present with severe pain on neck movement, subluxation, particularly .

of C_5 or C_6. can occasionally cause cord compression (Dieppe et al.. 1985). There is vertebral plate erosions. osteoporosis and nodules in or about the bodies of the vertebrae (Bland 1974).

2) Shoulder joint

According to Harris (1985). rheumatoid arthritis of the shoulder does not only affect the synovium within the gleno-humeral joint. but also involves the distal third of the clavicle. various bursae and the rotater cuff. together with multiple muscles around the neck and chest wall. The shoulder joint may be the seat of severe pain and limitation of movement in all directions (Dick and Goodacre. 1985). In cases of severely involvd shoulder. the muscles may be atrophied and the head of the humerus may be eroded and worn away to the point of not being palpable. large synovial cysts are occasionally encountered. presenting as displacement of the deltoid muscle by a cystic mass beneath. calci-fication within the bursal or muscle area (Berger and Ziter. 1972). Tears of rotator cuff have been reported (Weiss et al.. 1975)

3) Elbow joint :

Elbow joint involvement in rheumatoid arthritis is a common cause of disability on examination the elbow joint is often found to be incapable of a full extension. and in severely involved elbow joint there is also limitation of

flexion (Buchanan and Kean, 1986). palpation of the sulci on either side of the olecranon reveals synovial proliferation (Harris, 1985), leakage of synovial fluid from the olecranon bursa has been described as a cause of forearm oedema (Macfarlane and vander linden, 1981).

Bursae involved around the elbow joint must be distinguished from rheumatoid nodules in the antecubital fossa the epitrochlear nodes may be palpated and both the median and ulnar nerves may suffer entrapment at the elbow. (Dick and Goodacre, 1985).

4) Hand and wrist :

The wrist shows hypertrophy of its synovial lining with dorsal swelling within the tendon sheath of the extensor muscles (Harris, 1985).

Dorsal sublaxation of the ulnar styloid is a common deformity in the rheumatoid wrist. The ulnar collateral ligament is stretched by the hypertrophied synovium of the radioulnar joint until it is torn from its attechment to the ulnar styloid, this results in the distal end of the ulna sprining upwards (Buchanan and Kean, 1986).

Instability of the wrist may cause the carpus to sublux from the lower end of the radius towards the palm of the hand. This results in severe loss of grip power (Korin and tobis, 1971).

Flexortendons may become involved at the wrist and the median nerve may undergoes compression under the flexor retinaculum (Carpal tunnel syndrome), compression of the median nerve produces weakness and wasting of the thenar eminence. Sensory disturbance occur in the thumb. index middle and ring fingers.

Ulnar nerve entrapment at the wrist is less commonly and produces wasting of the interossei and muscles of the hypothenar eminence sensory symptoms may occur in the ring and fifth finger (Ranawat and Straub. 1970).

Ulnar deviation at the metacarpo-phalangeal joints often producing little disability (Barnes and Mason. 1975). Many factors combine to produce this deformity. but the major ones are alteration of the congruity of the articulating surfaces. displaced tendon and gravity (Dick and Goodacre. 1985). Zigzag phenomenon occuring between the wrist and the metacarpophalangeal joints is the best hypothesis for the explanation of ulnar deviation it is likely that ulnar displacement of the proximal row of the carpi and associated radial rotation of the distal carpi and metacarpals due to the relatively unopposed force of the radial carpal extensors and flexor muscles is followed by compensatory ulnar phalan - geal drift enhanced by the greater ulnar angulation of the flexor tendons as they emerge from the wrist (Shapiro. 1970).

In early disease the proximal interphalangeal joints may show marked soft tissue swelling, giving rise to the characteristic spindle-shaped deformity (Buchanan and Kean. 1986).

In more advanced disease a "swan-neck" deformity may occur. This consists of flexion of the metacarpophalangeal and distal interphalangeal joints with hyperextension of the proximal interphalangeal joint. The deformity is complex in its pathogenesis. tightness of the intrinsic muscles may be primary but more often is secondary to synovial hypertrophy or forward subluxation of the metacarpophalangeal joint which causes, the intrinsic muscles and tendons to be stretched tight. This "intrinsic plus" deformity as it is often called. causes. The metacarpophalangeal joints to flex as the fingers are extended, if there is laxity or destruction of the volar plate of the proximal interphalangeal joint. then hyperextension of this joint will occur owing to the tight interossei (Buchanan and Keen, 1985). flexion at the distal interphalangeal joints may be caused by the pull of the long profundus tendon which exceeds the pull of the extensor tendons which is bowstrung across the proximal interphalangeal joints (Buch and Kean, 1986) flexion of the distal interphalangeal joint may occur owing to avulsion of the distal phalangeal extensor tendon insertion with

resulting mallet finger deformity (Mccarty and Gatter, 1966). A mallet finger deformity may itself result in swan neck deformity (Litter and Eaton, 1967).

Boutonniere deformity, which entails hyperextension at the metacarpophalangeal and distal interphalangeal with flexion of the proximal interphalangeal joints occurs as a consequence of chronic inflammation of the proximal interphalangeal joint. The central slip of the extensor tendon is stretched or torn from its insertion into the base of the middle phalanx. This cause the proximal interphalangeal joint protrude upwards through the lateral extensions of the extensor tendon like abutton through a button hole, hence the term "buttonhole" or "buttonniere" deformity. The lateral fibres of the extensor tendons slip down on each side of the proximal interphalangeal joint and act as flexor of the joint (Litter and Eaton, 1967).

Casagrande (1965) has suggested that the buttonhole deformity may result from tautness of sublimis tendon, which is obstructd at the entrance to the flexor tendon sheath either by nodule formation or proliferative tenosynovitis.

The thumb is often very severely involved in rheumatoid arthritis. If the metacarpophalangeal joint is severly damaged the long and short thumb extensors are displaced volarwards on the ulnar side of the thumb. This causes loss

of extension of the metacarpophalangeal joint. Hyperextension of the distal phalanx no occurs due to tension on the long thumb extensor. This deformity is termed "Z" - shaped" deformity (Buchanan and Kean. 1986). Other deformities of the thumb may be found when there is severe disease of the carpometacarpal joint this causes volar subluxation of the first metacarpal. resulting in contracture of the adductor pollicis and adduction of the proximal thumb (Swezey. 1986).

Marked resorption of the bone of the finger joints can produce shortening and telescoping of the fingers the opera-glass or "main-enlorgnette" deformity so called because the finger can be extended and retracted by pulling on them (Dieppe et al., 1985).

5) Hip joint :

It is less involved in adult forms of rheumatoid arthritis than in juvenile type. Pain on the lateral aspect of the joint is often a manifestation of trochanteric bursitis rather than synovitis (Harris. 1985).

Patient with severe hip disease not only suffer from severe pain. but also have marked functional disability since they lose both abduction and rotation of the joint. (Dick and Goodacre. 1985).

The earliest and most common radiological finding in the

hips in rheumatoid arthritis is loss of joint space. (Duthie and Harris, 1969) in patients with severe hip involvement resorption and destruction of the acetabular side of the joint may occur, giving rise to protrusio acetabuli. (Buchanan and Kean. 1986).

Avascular necrosis of femoral head is not uncommon in patients with rheumatoid arthritis, especially those being treated with corticotrophin or oral corticosteroid therapy avascular necrosis is probably results from the collapse of the osteoporotic bone in the femoral head. (Sweetnam, et al., 1960).

Cysts occasionally arise from the hip joint similar to Baker's cysts behind the knee. these have been found to contain fibrovascular tissue (Cotton and Darby, 1970).

6) Knee joint :

In the Knee. synovial proliferation is more profuse than in any other joint,involvement in the suprapateller pouch leads to bulky swelling and accumulation of large volumes of synovial fluid, meniscal cartilages may be destroyd. and loss of the cruciate ligaments to the proliferative pannus leads to instability in an anteroposterior direction. (McGurie and Harris, 1979).

Very early in rheumatoid arthritis of the Knee joint there is effusion, quadriceps atrophy and loss of full

extension. (Gupta, 1970). Minimal Knee joint flexion deformities can be corrected if detected early enough, but if they have been present for several months only 50 % will be completely corrected, and the relapse rate is high (Convery, et al., 1971) flexion of the Knee increase markdly the intra-articular pressure and may produce an outpouching of posterior components of the joint space (Golding, 1982).

A large popliteal cysts may retard venous and lymphatic flow, producing signs of thrombophlebitis, with sudden rises in pressure within the Knee, the cyst may herniate along muscle planes in the calf or even rupture into the calf. An ecchymotic area around the lateral mallelous called the "crescent sign" may be seen shortly after rupture and diagnosis can be confirmed by arthrogram (McGuire and Harris, 1979). Also gastrocnemius and semimembranosus bursae may become enlarged and tender (Buchanan and kean, 1986).

Nodules tend to form in some patients along the patella at sites of tendon insertion usually they are not large and not symptomatic. other complications include bony pseudocyst formation secondary to the rheumatoid process with pathologic fracture (Gohel et al., 1972). spontaneous rupture of the infrapatellar tendon (Razzano, et al., 1973).

7) Ankle joint :

The ankle joint is less commonly affectd than other joints, possibly due to its relative paucity of synovial tissue, pain in the region of the ankle joint may be due to inflammation of the peroneal tendon sheaths and achilles tendon bursa or may be caused by involvement of the mid-tarsal joints, when the ankle joint itself is involved there is local tenderness on pressure over the joint margin, and pain is felt particularly on flexion and extension. (Dick and Goodacre, 1985).

The tendoachilles may show diffuse granulomatous inflammation or rheumatoid nodules may develop within it. spontaneous rupture of the tendon have been reported (Rask, 1978).

Inflammation in the achilles tendon bursa may be evident radiologically as erosions of the posteriorsuperior aspect of the calcaneum (Dick and Goodacre, 1985).

The subtalar or talocalcaneal joint is commonly involved in rheumatoid arthritis (Dixon, 1971). Subtalar arthritis limited inversion and eversion of the ankle, severe involvement of the talonavicular joint leads to a painful valgus deformity of the foot subtalar joint disease results in malalignment of the true ankle joint and alters gait. There is lack of planter flexion at heel strike and there is a late

heel rise. (Buchanan and Kean, 1986). In severe cases of subtalar disease, the gait of the rheumatoid patient is reduced to a shuffle. (Marshall, et al., 1980).

8) Feet :

The feet are frequently involved in rheumatoid arthritis. The most common joints to be affected are the lateral metatarsophalangeal joints (Vidigal, et al., 1975).

With destruction of the metatarsophalangeal joints. The toes become subluxed upwards on the metatarsal heads. The toes become clawed and the fat pad under the distal phalanx slips backwards so that painful callosities develop over the undersurface of the distal parts of the toes. The patient often describes the pain over the metatarsal heads as they were walking on pebbles (Buchanan and Kean, 1986).

Long-standing disease is characterised by marked deformities of the fore-feet, with hallux valgus and packing together of the lateral toes, which may override or underride the hallux or each other (Dixon, 1971).

Temporomandibular joint :

Temporomandibular arthritis may be unilateral or bilateral and may develop early in life as part of a juvenile polyarthritis (Carlsson, et al., 1978).

Pocket and surface erosion, flattening and marginal proliferations correlated well with limitation in opening the

mouth, stiffness, referred pain, tenderness on biting and crepitus (Chalmers and Blair, 1973).

Circoarytenoid joint :

Involvement of the circoarytenoid joints occurs more frequently in rheumatoid arthritis than is generally realised. Hoarseness, pain radiating to the ears, fullness of the thorat on swallowing or speaking, and dyspnoea are prominent symptoms laryngoscopy often reveals inflammatory swelling of the arytenoid cartilage and vocal cords. (Buchanan and Kean, 1986), Hoarseness may be due to ischaemic recurrent laryngeal nerve paresis (Wolman, et al., 1965) or to rheumatoid nodules of the vocal cords (Webb and payne, 1972).

Manubriosternal joint :

Tomography of the manubriosternal joint has revealed erosions in approximately three - quarters of patients (Kormano 1970). Subluxation or dislocation of the manubriosternal joint can occur (Wiseman, 1981). Although this is a cartilaginous joint, synovial lining can develop as a result of abnormal movement (Buchanan and Kean, 1986).

II. Systemic manifestations :

1) Granulomatous nodules :

Perhaps the commonest non-articular manifestation of rheumatoid arthritis is the granulomatous nodule, which is characteristically found near the olecranon process in 20-30%

of patients with "definite" or "classical" rheumatoid arthritis as defined by the American Rheumatism Association (Ropes et al., 1959).

They are firm, round, non tender and often multiple with characteristic histological features. Subcutaneous nodules favour the elbow, head, sacrum and Achilles tendon, usually they are mobile but they may, particularly around the elbow, become bound to periosteum. Intracutaneous nodules appear around the fingers. Nodules in tendons cause functional disturbance and are often responsible for triggering of fingers when they form inside flexor-tendon sheaths. Nodules in internal organs, particularly lung, heart and eye, can cause serious functional impairment (Dieppe, et al., 1985).

Rheumatoid nodules may develop rapidly and persist unchanged for many months or years (Buchanan and kean, 1986).

Excision of granulomatous nodules is rarely helpful since they nearly always recur, suppression of the disease by drugs or a spontaneous remission, is often associated with nodules becoming softer, smaller or disappearing altogether, occasionally, in sites such as the ball of the foot or over the sacrum, nodules break down and discharge - a complication known as fistulous rheumatism (Dieppe, et al., 1986)

Nodules are associated with high titres of circulating IgM rheumatoid factor (Kellgren and Ball, 1959). However,

rheumatoid nodules have occasionally been reportd in individuals with only mild evidence of synovitis who are seronegative by conventional laboratory tests for rheumatoid factor (Belin et al., 1979 and Brown et al., 1979).

2) Vasculitis :

Rheumatoid vasculitis is usually more common in males and generally only occurs in patients with severe destructive, seropositive nodular disease of several years duration (Ansell and loewi, 1977).

The mild form of vasculitis presents as small brown periungual and finger-pad lesions or splinter haemorrhages which come and go and are often unnoticed by the patient. These are due to occlusive vasculitis and are certainly not associated with a bad prognosis and require no treatment, when larger vessels are involved, skin ulceration, peripheral neuropathy, mononeuritis multiplex and gangrene of a digit or extremity may occur. Severe necrotising vasculitis presents and behave much like polyarteritis nodosa and death may result from bowel perforation or myocardial infarction. (Dieppe et al., 1985).

Buchanan and Kraag (1980) found leg vein Thrombosis more common in patients with osteoarthritis than rheumatoid arthritis. They suggested that aspirin therapy may account for this protective effect in rheumatoid arthritis, but recent work by kean et al., 1984) has shown that gold sodium

thiomalate in therapeutic concentrations has anti-thrombin activity, and may also explain the lower incidence of leg vein thrombosis in rheumatoid arthritis.

3) Peripheral neuropathy :

Patients with severe rheumatoid arthritis may develop a peripheral neuropathy. This neuropathy may be a mild distal sensory neuropathy or a severe fulminating sensorimotor neuropathy (Chamberlain and Bruckner, 1970).

Rheumatoid neuropathy is usually symmetrical, occuring in the upper limbs or in the legs. Mononeuritis or mononeuritis multiplex is a classical, , (Buchanan and Kean, 1986).

Vasculitis involving the vasa nervosa has been generally agreed to cause ischemia of the peripheral nerves, but toxic or metabolic factors may also be responsible (Haslock et al., 1970).

Immunofluorescent techniques has shown immuneglobulin deposits in a small porportion of the peripheral nerves (Beckett and Dinn, 1972).

Neuropathy may also occur in patients with rheumatoid arthritis due to chrysotherapy or to treatment with chloroquine, (Dick and Goodacre, 1985).

Neuropathy is possibly more frequent in patients treated with long-term high-dosage systemic steroids, and there is

evidence that abrupt cessation of steroids may precipitate it. (Golding, 1982).

4) Muscle changes :

Most patients develop localised muscle weakness and wasting around inflammed joints thought to be due to reflex inhibition secondary to the inflammation, about one-third develop proximal and distal atrophy far from joints and this has been attributed to myositis. muscle biopsy shows a whole range of non-specific abnormalities often associated with vasculitis, patients on steroids also develop proximal muscle weakness making it difficult to rise out of chairs and mount stairs, (Dieppe et al., 1985).

Electromyography has shown a minor degree of polymyosities especially in severe cases (Currey, 1975), which is manifested clinically by muscle pain, tenderness, induration and muscle weakness, later on there will be contracture or muscle shortening (Ansell, 1978).

5) Gastrointestinal tract :

Binder et al (1966) found no evidence of small bowel dysfunction, as shown by normal histological appearances. However, Marcolongo et al (1979) reported partial or complete loss of superficial epithelium and gland cells, intense infiltration of the lamina propria and intestinal tissue by lymphocytes, plasma cells, and granulocytes, and vasculitis

lesions, in gastric, colonic and rectal biopsies obtained from patients with rheumatoid arthritis.

Minor biochemical abnormalities of liver function are frequent in patients with rheumatoid arthritis, and occasional patients may have mitochondrial autoantibodies (Webb et al., 1975).

Hepatomegaly with lymphocyte and plasma cell infiltrate, bromosulphthalein retention and raised alkaline phosphatase levels are common and may mark hepatic involvement in rheumatoid arthritis and sjogren's syndrome (Dick and Goodacre, 1985). Amyloid deposition may cause striking hepatomegaly. Agoldrelated hepatocellular necrosis has been described and salicylates may also adversely affect liver function (Dieppe et al., 1985).

Xerostomia may develop as part of Coexisting sjogren's syndrome, in patients with severe xerostomia the lips develop painful fissures and the tongue becomes red and painful (Buchanan and Kean, 1986).

5) Pulmonary involvement :

Although rare, pulmonary involvement in rheumatoid arthritis is important, five pleural and pulmonary lesions are recognised (Walker and wright, 1968).

a) Pleurisy with or without effusion is a very common finding at autopsy although its manifestations during life is

less frequent (Walker and Wright, 1968). Pleural tissue from patients with rheumatoid arthritis and pleuritis is capable of producing IgM and IgM rheumatoid factor. This suggests that local events may contribute to the pathogenesis of rheumatoid pleural disease (Halla, et al., 1983).

b) Caplan's syndrome : consists of nodular opacities varying in size from 0.5-5 cm throughout both lungs in a patient with rheumatoid arthritis. The radiological appearance is of nodular opacities against a background of minimal pneumoconiosis. (Buchanan and Kean, 1986).

c) Chronic interstitial pulmonary fibrosis although extremely rare, is sometimes a fatal complication of rheumatoid arthritis (Thompson, 1965) it manifests clinically by cough, dyspnoea, chest pain pleuritic and non - pleuritic, and haemoptysis. Approximately 10 % of patients are asymptomatic (Patterson et al., 1965). On chest x-ray reticulation and mottling are most marked at the lung bases cystic changes with honeycomb appearance in severe cases, and pneumothorax may occur owing to rupture of a cystic bulla (Rubin et al., 1967).

d) Pulmonary rheumatoid nodules may occur at any time in the course of rheumatoid arthritis and have even preceded. The onset of arthritis. (Hull and Mathews, 1982). Cavitation of nodules may be followed by rupture into the pleural

cavity and pyopneumothorax (Crisp et al., 1982) finger clubbing has been reported with pulmonary rheumatoid nodules (Buchanan and Kean, 1986).

e) Pulmonary artery involvement : Arteritis of the pulmonary artery is very rare but may result in pulmonary hypertension (Jardan and Snyder, 1965).

7) Cardiac involvement :

Clinical heart disease attributable to rheumatoid arthitis is uncommon (Golding, 1982).

Pericarditis, myocarditis, and valvulitis may occur either separately or as pancarditis (Thompson, 1966).

Pericarditis usually develops after rheumatoid disease has been established, rarely it may preceed arthritis the majority of these patients are seropositive (Harris, 1985)..

Granulomatous infiltration of the myocardium and conducting system may rarely occur and lead to conduction defects, cardiac arrhythmias and acute myocardial failure. Granulomatous involvement of the valves may lead to valvular insufficincy (Carpenter, et al., 1967).

Coronary arteritis may also occur and may be complicated by myocardial infarction (Swezey, 1967).

8) Ocular manifestations :

Episcleritis is relatively common, and results in mild, often intermittent, ocular pain and injection of the eye and

usually resolves leaving no permanent sequelae. (Buchanan and Kean, 1986).

Scleritis is much more severe than episcleritis and may lead to visual impairment and even blindness. The entire uveal tract is inflamed and anterior synechiae may form with the risk of subsequent closed angle glucoma. Thinning of the sclera may occur in severe scleritis, and may cause exophthalmos (Kennedy and McGavin, 1975).

Scleromalacia perforans results from necrosis and sloughing of a rheumatoid nodule situated in the sclera leaving a punched - out hole through which the black uveal tract may be seen. (Buchanan and Kean, 1986).

Kerato conjunctivitis sicca occurs in approximately 10-15 % of patients with rheumatoid arthritis. The patients complain of dryness and grittiness. The dryness of the eyes is due to chronic inflammation of lacrimal and mucous-secreting glands of the eye. Diagnosis of Kerato-conjunctivitis sicca is based on an abnormal schirmer tear test, rose bengal staining of the conjunctivae and slit lamp examination which shows punctate of filamentary keratitis. (Dick and Goodacre, 1985).

9) Lymphadenopathy :

Local lymphadenopathy is common in the region of an inflamed joint (Buchanan and Kean, 1986). The nodes are

discrete and non tender, and histologically reveal non specific inflammatory changes (Nosanchuk and Schnitzer, 1969).

Generalised lymphadenopathy, although common in still's disease, is rare in adult, and reticulosis should be excluded first since tumours of the reticuloendothelial system occur more commonly in patients with rheumatoid arthritis (Lea, 1964).

The lympho-reticular distrubance may be exagerated in a variety of rheumatoid arthritis known as "felty's syndrome" in addition to generalised lymphadenopathy, we get splenic enlargement and Thymic enlargement (Gardner, 1986).

10) Anaemia and other Haematologic changes :

Anaemia is very common in patients with rheumatoid arthritis and is usually of the normochromic normocytic variety (Dick and Goodacre, 1985). . The serum iron is usually low, but the total iron binding capacity is commonly normal, or low normal or low (in contrast to the increase in iron deficiency anaemia). The red cell survival time and the absorption of oral iron is normal, (Barnes, and Mason, 1975). but the plenty of sequestered iron can be demonstrated in the marrow, synovium and lymph nodes (Dieppe, et al., 1985).

The pathogenesis of Anaemia is obscure, it seems likely that there is some degree of malutilization of iron and possible also a failure of haemoglobulin protein synthesis

(Blake, et al., 1981). Interestingly, the erythropoetin concentration has been found to be low in rheumatoid arthritis (Williams et al., 1982).

Hypochromic microcytic iron deficiency anaemia may also occur in rheumatoid arthritis especially in females, and chronic loss of Blood from the gastrointestinal tracts due to aspirin and other anti-in-flammatory drugs may be a contributory factor. This anaemia respond to iron therapy (Dick and Goodacre, 1985).

Rarely macrocytic (megaloblastic) anaemia occurs in rheumatoid arthritis and may be due to folic acid deficiency or anaemia may form part of felty's syndrome (Barnes and Mason, 1975).

11) Bones :

Periarticular and generalised osteoporosis is a common feature of rheumatoid arthritis. The pathogenesis of generalised osteoporosis is multifactorial, involving duration of disease, age and sex of the patient, and use of corticosteroid drugs (Muller and jurist, 1973).

Recent studies suggest that patients with rheumatoid arthritis may have hypercalcaemia and secondary hyperparathyroidism, plasma zinc concentrations are depressed in patients with rheumatoid arthritis and may be related to the pathogenesis of osteoporosis (Kennedy, et al., 1975).

Rarely massive osteolysis may occur in rheumatoid arthritis (Williams, et al., 1966).

Investigations of Rheumatoid Arthritis

A) Laboratory investigations :

The laboratory findings in rheumatoid arthritis are those of a chronic inflammatory disease. No specific laboratory test exists for this condition, yet a constellation of laboratory findings can aid the experienced clinician in arriving at a diagnosis and in management. (Baum, and Ziff 1985).

I) Hematologic studies :

1. Erythrocytes :

Haemoglobin value has been incorporated into most schemes for evaluation of rheumatoid disease. it is objective, accurate, and correlates well with disease activity, gradually returning to normal level as the patient goes into remission, even though no haematinics are given. Also haemoglobin concentration can be correlated with the erythrocyte sedimentation rate, but there is usually no correlation with the duration of the disease (McCarty, 1979).

The plasma iron value is low in the presence of active disease and there is an inverse correlation between, The plasma iron value and the erythrocyte sedimentation rate. (Mowat et al., 1969).

The total iron binding capacity is much lower in

rheumatoid arthritis although it is usually higher than normal in simple iron - deficiency anaemia. (Johansson and Strandberg, 1972).

The refractoriness of the anaemia in most patients to oral iron therapy is in accord because absorption of iron is usually normal (Baum and Ziff, 1985).

A longitudinal study found that serum ferritin levels rose during active synovitis and fell during remission. The highest levels were found in patients with systemic complications (Blake and Bacon, 1981).

The plasma volume in patients with R.A. is greater than normal the basis for this increase is not well understood. A compensatory increase in plasma volume for a reduced corpuscular volume is probably one factor. (Baum and ziff, 1985).

2) Leukocytes :

White blood cell counts are usually in the normal range or are only slightly elevated (Baum and ziff, 1985) Leukocytosis is common in juvenile R.A. (Lindjberg, 1964) leukopenia is rare in R.A. when present, it is more likely to be observed in the chronic state of the disease (Baum and ziff, 1985). The leuckopenia and splenomegaly of felty's syndrome may reflect the uptake of immune complexes by circulating polymorphonuclear cells and the subsequent

removal of these cells by the spleen (Hurd and cheatum, 1976). Another possible cause of the leukopenia is the uptake and destruction of polymorphonuclear leukocytes with attached complement-fixing antineutrophil antibodies (Wiik and Munthe, 1974).

The differential white blood cell count is usually within normal limits, but polymorphonuclear leukocytes may be increased in more acute cases. (Baum and ziff, 1985).

Neutrophilia may occur with corticosteroid therapy but the possibility of bactrial infection, particularly the relatively symptomless super-infection of a damaged joint should be remembered. polymorph cell count is frequently used to monitor anti-rheumatic drugs, inspite of its little value in assessing disease activity (Bacon, 1982).

Neutropenia in R.A. has been divided into two types, one associated with splenomegaly (Felty's syndrome) and another without splenomegaly but with an increased frequency of circulating immune complexes (Bucknall, et al., 1982). The possibility that drugs, such as gold salts, penicillamine, phenylbutazone and related drugs, and immunosuppressive agents, are the cause must be remembered. Eosinophilia is not uncommon in R.A. (Baum and ziff, 1985) Eosinophilia is usually interpreted as a sign of drug allergy most commonly to gold and penicillamine therapy. with gold therapy

eosinophilia and a coincident rise in serum IgE levels have been shown to be reliable warning signs of the development of other more serious side effects (Davis and Hughes, 1974). Eosinophilia may also develop in occasional patients with severe, destructive arthritis and a high incidence of vasculitis, pleuritis and subcutaneous nodules. These patients have immunological evidence of severe disease and it has been suggested that eosinophilia is an immunological response (Panush, et al., 1971).

Lymphocytes :

In recent years, many have been interested in the function of the subpopulations of lymphocytes in various diseases. for the most part. the percentage of B,T., and null cells in the Blood in R.A. have been in the normal range (sahud and Cohen, 1971k. Tannenbaum and Schur, 1974).

In early R.A. of under 3 months duration, the defect was due to a decreased generation of suppressor "T" cells accompanied by a decrease in the B - Cell response. In a study of patients with disease activity of more than 12 month's duration, the "T" cell response was normal, but the "B" -cell response continued to be deficient (Sakane, et al., 1982), over all, mitogenic transformation of R.A. lymphocytes appears to be decreased (Baum and ziff, 1985).

Barada et al. (1981) found a specific defect in monocyte spontaneous cytotoxicity that correlated with rheumatoid disease activity.

3) Platelets

Thrombocytosis is a common finding in acute and severe rheumatoid arthritis it correlates with most parameters of disease activity such as erythrocyte sedimentation rate, rheumatoid factor, and acute phase reactants (Farr, et al., 1983) but if the platelet counts is greater than $1,000,000/mm^3$ an alternative cause of the thrombocytosis should be considered (Buchanan and kean, 1986).

Thrombocytopenia is not a feature of rheumatoid disease, except in felty's syndrome, or as a result of gold (Kean and Anastassiades, 1979). and D-penici-llamine therapy (kean, et al., 1980).

II. Acute phase Reactants :

These substances found in blood reflect the presence and degree of inflammation. because their serum concentration reflects the activity of the disease, they are useful in therapeutic management. A discrepancy often exists, however, between the clinical disease severity and the magnitude of the acute-phase response. for this reason, a change in the level of an acute phase reactant is often of greater significance in guiding therapy than the actual level itself. (Baum and ziff, 1985).

1) Erythrocyte Sedimentation Rate :

The E.S.R. usually is elevated and parallels the activity of the disease. Exacerbations are usually accompanied by an increase and remissions by a decrease in the ESR. in complete remission, the values usually become normal (Baum and ziff, 1985).

It must be emphasised that a normal E.S.R. does not exclude the presence of the disease and very high values may be encountered in normal persons with no evidence of any disease after extensive evaluation. (Zacharski and Kyle, 1967).

The plasma components that influence the E.S.R. most are fibrinogen and alpha and gamma globulin (Baum and ziff, 1985).

Also alterations in the shape and size of the red blood cells influence the ability of these cells to form rouleaux and thus inturn influence the E.S.R. thus anaemia, both microcytic and megaloblastic seen in rheumatoid disease, is associated with a rapid fall in the E.S.R. (Kushner, 1981).

Normal values of E.S.R. are 15 mm. / hour for males and 20mm / hour for females (Hayes and Stinson, 1976) There are physiological age and sex variations in the E.S.R. also seen among smokers, women taking contraceptive pills and pregnant women (Golding, 1982).

E.S.R. is useful in follow up of longterm disease modifying drugs, as gold and penicillamine, but seems uninfluenced by short acting non-steroidal anti-inflammatory drugs. E.S.R. is returning towards normal in those cases treated with corticosteroids (Mc Conkey, et al., 1979).

2) C- Reactive Protein :

Practically C-reactive protein (C.R.P.) is present in all patients of R.A. with clinical evidence of disease and usually parallels the ESR closely (Baum and ziff 1985). Treatment of R.A. with nonsteroidal antiinflammatory drugs produced no significant change in the ESR or the CRP after 12 weeks of therapy (Amos, 1978). The CRP was found to be a more sensitive test because gold, penicillamine, and prednisone had a greater effect on the C.R.P. than on the E.S.R. (Walsh, et al., 1979).

Nusinow and Arnold (1982) reported that the CRP correlated with erosive disease in 37 patients with RA who never received corticosteroids, not even as joint injections. These researchers believe that CRP levels above 5 mg/dl (Normal 0.6 mg/dl) predict erosions, and they regard the test as an indication to begin remittive therapy early in the course of the disease.

3)— Plasma viscosity (PV) : Plasma viscosity as an index of disease activity in RA is as reliable as the ESR or the CR.P.

The normal range for P.V. is independent of age and sex and the technique is rapid and simple (Pickup, et al., 1981).

III. Serologic Reactions and Complement Studies:

1) Rheumatoid factor :

Rheumatoid factor are autoantibodies directed against antigenic determinants of the F_c fragment of immunoglobulin G (IgG) molecules (carson, 1985). These autoantibodies are usually IgM, but occasionally IgG (Golding, 1978), sometimes IgA as well (Holborow, 1978).

There are five classes of immunoglobulins (Ig): IgG, IgM, IgA, IgD, and IgE, all having the same basic four chains structure : two light (L) and two heavy (H) chains but they differ in amino-acid sequence of their class specific "H" chains (Frangione, 1981). These chains are linked together by disulphide bonds (Golding, 1978). A proteolytic enzyme papain splits. The Ig molecule into three fragments : 2 of which retain the antigen binding property (Fab) and 1 fragment (F_c) or crystallisable fragment determines the biological properties of the various immunoglobulin molecules (Holborw, 1978).

Most methods developed for the measurement of antibodies against exogenous antigens has also been applied to the assay of rheumatoid factor. These include agglutination, precipitation, complement fixation, and immunofluorescence

assays, (Mc Cormick, 1963).

A positive Rose-waaler test may be more specific for R.A. than the bentonite or latex flocculation assays, since the latter detect antiallotypic antibodies resulting from transplacental immunization or transfusion, as well as true auto-antibodies, (Steinberg and Wilson, 1963).

According to the presence or absence of IgM rheumatoid factors in their sera, patients with rheumatoid arthritis are classified into seropositive and seronegative groups respectively (Hughes and Currey, 1975). The seronegative patients as well as the seropositive ones may have IgG and IgA rheumatoid factors (Holborow, 1978).

The sera of 75% of patients with RA contain IgM rheumatoid factor. This is often absent at onset, appears as the disease progresses and disappears again in long-standing disease or after treatment with disease suppressing drugs, levels fluctuate considerably and are not a reliable guide to disease activity. Persistently high titres are of some prognostic significance and tend to correlate with severe erosive disease and the presence of extra-articular features such as nodules, felty's syndrome and sjogren's syndrome (Dieppe, et al.,1985).

IgG rheumatoid factors are abundant in the sera, and the synovial fluids of many patients with severe rheumatoid

arthritis (Theofilopoulos, et al., 1974). These high levels returned to normal with clinical improvement (Elson, et al., 1983) unfortunately, the routine assay of IgG rheumatoid factors presents several difficulties (Carson, 1985).

Rheumatoid factors are not specific for R.A. rather, they are found in the sera of avariable portion of patients with acute and chronic inflammatory diseases, and in some apparently normal individuals. The exact incidence of rheumatoid factor in a population depends upon the assay system and the titre chosen to separate positive and negative factors (Carson, 1985). Other diseases in which positive rheumatoid factor tests are frequent include other rheumatic diseases, viral infections, chornic inflammatory diseases, and neoplasms after chemotherapy or radiotherapy (Twomey, 1976).

2) Antinuclear Antibodies :

These are antibodies directed against various cell nucleus antigens being neither tissue specific nor species specific (Aitcheson, et al., 1980).

In 1948 Hargraves and Colleagues initiated the study of antibodies to nuclei with the description of the (LE) phenomenon. The demonstration of the ingestion of Traumatized cells from SLE patients by polymorpho-nuclear leukocytes was readily confirmed and is now known to be due to the reaction

of antibodies against nucleoprotein (DNA-histone) with nuclei and the subsequent phagocytosis of such sensitized nuclei.

The next major advance was the indirect immunofluorescent assay for the detection of A.N.A. The assay detects antibodies with various antigenic specificities but is very useful as screening test.

The frequency of occurrence of ANAs in rheumatoid sera is approximately 40 % when measured by indirect immunofluorescence.

The most common staining pattern of fluorescence observed in patients with rheumatoid arthritis is the diffuse or patchy homogeneous pattern, which correlates with the presence of antihistone antibodies. The second most common pattern of staining in these patients is a speckled pattern, this includes a group of antibodies directed at nonhistone nuclear proteins (Sm, n-RNP, SS-B, Scl-70, and other unidentified antigens) (Notman, et al., 1975).

The nature of ANA in RA has recently received renewed attention, at least aportion of this ANA has been shown to have a dual specificity of great interest. surprisingly, the reactive antigen (s) for this ANA is contained in the Fc of IgG. Thus exhibiting rheumatoid factor activity, and is also contained in the core constituent of chromatin, the nucleosome, which is a DNA-histone complex (Agnello, et al., 1978).

3) Serum complement :

Serum complement levels in RA is usually either normal or elevated (Ellis and felix-Davies, 1959). Other researchers found that serum complement activity was reduced in patients with vasculitis, and the complement levels of seropositive patients were lower than those of seronegative patients (Mongan, 1969).

Reduced serum complement occurs in systemic seropositive disease in which complement-fixing circulating immune complexes are present (Weinstein, et al., 1972).

Assays of total hemolytic complement activity (CH50) are the best complement assays and should be employed if readily available, although assays of C4 and C3 are also useful. (Shapiro, at al., 1985).

IV. Studies of Liver Function :

Mild to moderate abnormalities of liver function have been reported in RA, but these have been confined mainly to tests of liver function that reflect serum protein synthesis. (Lefkovits and Farrow, 1955).

Serum alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), and serum glutamicpyruvic transaminase (SGPT) levels were normal, although 15% of patients showed an elevation of serum ornithine - carbamoyl transferase (Malmguist and Reichard, 1962).

Measurements of serum bilirubin and urine urobilinogen levels were within normal limits, but urine coproporphyrin excretion was elevated (Darby, 1953) decreased brom-sulphalein excretion was found in many patients (Castenfors, et al., 1964).

In RA, as in other inflammatory arthritides, The total cholesterol level is reduced. The mean reduction in sero positive patients was 53.7% in one series. The decrease was related to the severity and activity of the disease and was not affected by corticosteriod therapy (London, et al., 1963).

V) Studies of Renal Function :

Urinary abnormalities are uncommon in R.A. proteinuria and marked renal impairment should suggest the possibility of amyloidosis or analgesic nephropathy (Dick and Goodacre, 1985). Sorensen(1961) have reported a small to moderate decrease in the creatinine clearance in rheumatoid patients the average reduction was 36 %.

Serum creatinine concentration in RA, whether measured in patients with normal or impaired renal function, was lower than in matched controls, probably because of the smaller muscle mass of R.A. patients. (Nived, et al., 1983).

Impairment of glomerular filtration was related to the stage and duration of the disease and to the presence of

rheumatoid factor, but was unrelated to past history of drug intake including phenacetin (Baum and ziff, 1985).

VI. Synovial fluid Analysis :

Synovial fluid is a filtrate of plasma that passes through the fenestrations of subsynovial capillary endothelium into the extracellular space, where it joins with hyaluronic acid that is secreted by synovial cells and achieves an equilibrium with free fluid in the joint space, fluid in normal joint is present in small quantities sufficient to coat multiple folds of synovial membrane (Harris, 1985). Normal fluid is viscous owing to the high concentration of hyaluronate (Mc Carty, 1985) but in rheumatoid arthritis the viscosity is reduced. This may be attributed to enzymatic degradation of hyaluronate protein complex (Radian, et al., 1976).

The total protein of normal synovial fluid averages about 1.8 g/dl, in general the smaller protein molecules such as albumin are present in greater concentration than larger molecules such as the globulins (Mc Carty, 1985).

Normal joint fluid usually has only up to 50 W.B.C. per cubic millimeter but RA fluid usually has leukocytic counts from 2,000 to 75,000 cells / mm^3. polymorphnuclear leukocytes account for more than 50% (Schumaker, 1985). A great percentage of large mononuclear cells were found to be

lymphoblasts. These are relatively absent in crystal induced or septic arthritis (Traycoff, et al., 1976). lymphocytes are occasionally increased especially early in the inflammatory process (Gatter and Richmond, 1975). The granulocytes may contain inclusion bodies which represent phagocytosed immun complexes and small fibrinous bodies called rice bodies (Dippe, et al., 1985).

Crystals are usually absent in rheumatoid inflammation unless there is accompanying chondrocalcinosis (Shaprio, 1985).

Marked depression of joint fluid complement occurs in seropositive R.A., when sepsis and the crystal deposition diseases are excluded (Mc Carty, 1985).

Rheumatoid factors have been measured in synovial fluid in most instances, their titres,is identical to or slightly lower than that in the patient's serum in a few instances. They were found in the fluid and not in the serum and vice versa. IgG and IgM Rheumatoid factor titres are higher in RA fluids (Panush, et al., 1971).

B)- Radiology :

The small joints of the hand and feet are the earliest and most frequent sites of radiogrphic changes (Cone III, and Resnick, 1985). The arthritis may be a symmetrical in early stages, but as the disease progresses some degree of symmetry is usually evident (Cassidy, et al., 1967).

Osteoporosis is a charactristic feature of R.A. Early in the course of the disease, it tends to be localized to the juxta-articular region of the small peripheral joints. Later, generalized osteoporosis may be present in a few patients with R.A. osteomalacia may be observed. (O'Driscoll's and O'Driscoll, M. 1980).

Soft tissue swelling is usually evident radiologically early in the disease and is due to joint effusion, hyperplastic synovitis of joints and tendon sheaths, and periarticular oedema (Martel, et al., 1962).

After a variable peroid of time as the disease progresses, Marginal erosions occur at intra-articular sites that are not protected by overlying cartilage. Typically these "bar" areas are the initial points of attack by the proliferating synovial tissue. Compressive erosions occur when collapse of osteoporotic subchondral bone leads to invagination of one bone into another. These changes occur at articulations exposed to strong muscular actions or significant weight-bearing forces.the most characteristic site of compressive erosion is the hip, other important sites are at the metacarpophalangeal joints, where collapse of the base of a proximal phalanx by a metacarpal head produces a ball-in-socket-type articulation, and the radiocarpal joint of the wrist, where the scaphoid may appear to be

"countersunk" into the distal radius. The third type of erosion is surface resorption, usually related to inflammation of an adjacent tendon sheath. e.g. erosion of the outer margin of the ulnar styloid process, due to extensor carpi-ulnaris tenosynovitis (Cone III and Resnick, 1985).

Large cysts, or geodes, may form in the subchondral bone where joint fluid is pumped through small defects in the damaged cartilage, particularly in the large weight-bearing joints (Dieppe, et al., 1985).

In late disease, widespread cartilage destruction, subluxation and deformity are the dominant features (Dieppe, et al., 1985). Sclerosis of bone ends is often present afer the cartilage is destroyed particularly in weight bearing joints sclerotic area is indistinct and marginal bone formation is usually absent or minimal. Bone ankylosis of the tarsal or carpal joints, may be observed (Martel, et., 1965).

Involvement of the cervical spine is usually diagnosed by x-ray examination. lateral x-rays in full flexion and extension are essential, and an anteroposterior view of the occipitoatlantoaxial region through the open mouth is very useful (Bland, 1974) atlantoaxial subluxation and multiple subluxation of c 2-3, c 3-4, and c 5-6 are very characteristic of involvement of the cervical spine by R.A

separation of the anterior surface of the odontoid peg from the posterior sufrace of the anterior arch of the atlas by more than 2.6 mm in females and 3 mm in males is pathological (Bland, et al., 1965).

C)-Radionuclide joint imaging (isotopic methods)

The use of the radioisotope uptake scan in the assessment of inflammatory joint disease continued to be a topic of interest. The scan appeared to be the most sensitive indicator of active disease (Weissberg, et al., 1978).

In arthritis, localization of 99mm technetium labeled bone-scanning agents results primarily from the increased blood flow to the juxtra-articular bone that accompanies synovitis and cartilage degeneration (Paradis and kelly, 1975), additional contributors to increased bone localization of 99mm technetium labeled phosphates include capillary permeability, extraction efficiency and possibly binding into organic components of bone matrix (Genant, 1985).

Radionuclide imaging aided assessment of early or a typical seronegative rheumatoid disease as well as assessment of therapeutic response (Mxfield et al., 1972).

D)-Arthroscopy :

Arthroscopy is the endoscopic examintaion of the interior of a joint and therefore can provide more direct diagnostic information than any other ancillary procedure (Mc Ginty, 1985).

The great advantage of arthroscopy in assessing disease activity is therefore that the majority of the surface synovium may be visualized whereas only a small fraction of the total amount may be examined histologically (Yates and Scott, 1975).

Arthroscopy is particularly helpful in patients with estabished rheumatoid arthritis who develop a changing pattern of symptoms in a knee, failure to respond to injection of corticosteroids should strongly suggest a superimposed mechanical problem. (Shapiro, et al., 1985).

E)-Synovial Biopsy :

While adequate specimens of synovial tissue may be obtained in the majority of cases by blind needle biopsy, the most accurate method of synovial biopsy remains by arthroscopy where material is obtained under direct vision. in chronic rheumatoid disease, large masses of organized fibrin (rice bodies) exist within the joint space. If the blind needle biopsy,technique is used ,it is often impossibleto know at the time of biopsy, whether a piece of true synovium has been obtained or whether the biopsy material consists only of organised fibrin (Yates, 1978).

Synovial membrane findings of villous proliferation, superficial fibrin, markd lining cell increase, focal necrosis, plasma cells, and lymphoid follicles may strongly suggest rheumatoid arthritis but are not specific. in R.A. as

with several other systmic rheumatic diseases, diagnosis is often made by accumulation of criteria. Even if not giving a definite diagnosis, synovial biopsy by illustrating the presence or absence of inflammation may help guide symptomatic treatment, (Schumacher, 1985).

F)-Arthrography :

Arthrography is the technique of radiographic visualization of intra-articular anatomy after arthrocentesis and instillation of a contrast agent. Radio opaque contrast medium may be used alone (Single or positive contrast) or with injected air or CO_2 (double contrast), (Namey, 1985).

Arthrography can be used in rheumatoid arthritis to differentiate between a ruptured popliteal or Baker's cyst and acute thrombophlebitis. (Harris, 1981).

g)-Thermography :

The development of modern thermography represents an interesting study in the application of technology. in 1949, Horvath and Hollander, demonstrated the correlation between intra-articular temperature and clinical activity of the joint in patients with rheumatoid arthritis, skin temperature lower than the tissue beneath it, is determined by the blood flow, the metabolic activity, and external temperature, this difference at the knee was shown by Hanson to be between 4 and 5 ^{o}C. These facts form the basis for clinical assessment

of inflammation by thermography. (Namey, 1985). (Collins, et al., 1974) have described a complicated "Thermographic index" for normal joints, a basis for comparative thermographic assessment of inflammatory activity in joint disease. but noted that there is a durinal variation in the thermographic index. It has been used successfully in measuring the articular response to steriod injections, oral nonsteroidal drugs, pencillamine, and cytotoxic drugs (Bacon, et al., 1976).

Modern emission thermography, utilizes equipment capable of 0.1^{o}C temperature discrimination. This precision is available using modern electronic telethermography which must be performed in atemperature controlled room. A second less precise method of Thermography more widely utilized employs a device for liquid crystal thermography (L.C.T.) (Namey, 1985). Phase transition with temperature is charaterized by specific color-temperature response allowing color thermography applications with color-temperature gradients of 0.2 to 0.4 ^{o}C in the most sensitive response zone (Crissy et al., 1970).

Recently. these liquid crystals have been embedded in elastometric sheets, allowing for convenient application of thermographic studies at lower cost. The area of study is restricted to the area covered by the liquid crystal sheeting (Namey, 1985).

Management of Rheumatoid Arthritis

Proper management of R.A. results in the maintenance or restoration of the patient to a state of useful and harmonious function with her environment. Implicit is the relief of pain, the prevention of joint destruction, and the preservation or improvement of the patient's functioning (Ruddy, 1985).

1. Supportive Measures :

Once the diagnosis of rheumatoid arthritis has been made, the physician begins the process of informing the patient about her disease (Kay and Hammond, 1978).

The patient should be told that rheumatoid arthritis is a chronic, lifelong disease and that a variety of measure in the aggregate, can lead to significant improvement, that is to "control" of the disease (Lightfood, 1985).

Patient can be told that even if there is no "cure" for rheumatoid disease, the prospects are good and even if the disease does not settle spontaneously, the likelihood is that modern treatment can bring it under control. (Corbett, 1986).

Rest and Physical Therapy :

The optimal amount of rest varies from patient to patient, in general for patients with persistently active

disease of recent onset or with "uncontrolled" inflammation at any point, a two-to three-week period of inpatient hospitalization is desirable. for patients with mild disease, a period of two to four hours in the afternoon at the time of onset of fatigue with vocational responsibilities. The stiffness that follows periods of immobility should not dissuade patients from resting. (Lightfoot, 1985).

Although there may be controversy about the usefulness of complete bed rest in treatment of rheumatoid arthritis, there is widespread agreement about the utility of local joint rest. Naturally enforced rest, such as paralysis of an extremity from a stroke, poliomyelitis or peripheral nerve lesion, usually results in sparing of the paralyzed joints in patients who subsequently develop R.A. (Bland and Eddy, 1968, Glick, 1967). and Kammerman, 1966).

In R.A. The effective synovial blood flow of inflammed joints is reduced because of this relative ischemia, the increased metabolic demand during joint use may cause microinfarcton of synovial villi. Rest not only diminishes systemic stress but also decrease local oxygen demand in these ischemic joints. (Cheung, et al., 1980

Joint trauma can also be minimized by the use of splints. Regular adjustment of splints may even permit their use to correct deformity resulting from spasm and

inflammation. use of splints instead of casts at night and at rest periods also allows the limbs to be freed for the daily range of motion exercises. (Gault and spyker, 1969).

Instruction in proper positioning of joints during rest or sleep is equally important in preventing contracture, patients should rest on a firm mattress and have only one pillow at night. The patient should attempt to sleep in a position as near as possible to the anatomic, that is, with Knees and elbows fully extended and with the neck and wrists in a near-neutral position (Lightfoot, 1985) exercise to increase range of motion is best done when pain and stiffness are minimized by medication,analgesic physical modalities, and Time of day (Downey, 1985).

Any exercise prescribed to maintain muscle strength and range of motion should minimize stress to the affected joints because such stress aggravates the inflammatory process (Partridge, and Duthie, 1963). Gentle isotonic or isometric exercises are preferable. vigorous exercises should be porhibited (Castillo, et al., 1965). Any exercise that cause discomfort persisting for more than anhour or two should be decreased in amount. As the disease remits and physical tolerance increases. The exercise program can be escalated to include progressive resistive exercises (Lightfoot, 1985).

The application of heat or cold to involved areas is

often helpful, in relieving pain and muscle spasm. The form of heat used should be simple and available at home, frequently hot baths, showers, or soaks are the easiest. Baths allow the patient to use the buoyancy of the water to begin active range of motion exercises. (Downey, 1985). Cold applications are preferred if the inflammation is intense, as local hyperemia is already maximal (Lightfoot, 1985). In fact, there is some doubt that deep heating should be used in treating articular problems, there is evidence that the normal intra-articular temperature is lower than body tempera-ture,and further that, an increase of 5°C increases enzymatic lysis of human cartilage by rheumatoid synovial collagenease, suggesting that increased temperature may accelerate cartilage destruction (Feibel, and fast, 1976).

Occupational Therapy and Rehabilitation :

The world Health organisation defines rehabilitation as "the combined and co-ordinated use of medical, social, educational, and vocational measures for training and retraining the individual to the highest possible level of functional ability". (Chamberlain, 1986).

Arudimentary assessment of the patient's functional capacity should be conducted by the physician in the intial evaluation of the patient. A much more detailed and meaningful analysis of the interaction between the patient and her

environment can usually be accomplished by an occupational therapist, who has had special training in methods for such analysis (Ruddy, 1985).

No assessment of domestic activities or function at work is realistic until pain and stiffness are brought under control by non-steroidal anti-inflammatory drugs or by long-term antirheumatic agents (Chamberlain, 1986).

The occupational therapist will provide advice regarding joint protection, splinting, assistive devices, facilitation of activities of daily living (dressing, eating, housekeeping, etc.) and recreation. (Katz, 1985). observation of the patient at work, either in a simulated environment, e.g. Kitchen, carpentry shop, or directly in the home or on the job, may indicate unique problems requiring the construction of special appliances designed to deal with the problem. Attention to such details may make the difference between dependence and independence or between disability and Keeping a job (Cochrane, 1982).

Interaction with a vocational or rehabilitation counselor needs to be begun early in the contact with the patient, so that decisions regarding long-term outlook for continued employment can be arrived at gradually and realistically. while retraining of each patient into a position particularly adapted to her joint problems is an

indeal goal. on the other hand, vocational counselors often prevent disability by identifying and removing impediments to work that are unrelated to the actual performance of the job itself e.g. transportation to and from work. As an alternative the patient can be helped to accept partial disability in a supportive yet realistic way (Ruddy, 1985).

II) Medical therapy :

Drug therapy forms only part of the overall management of a patient with rheumatoid arthritis, it may be the most effective, it may also be the most disastrous (Holt, 1986).

There is no drug treatment which is both effective and completely safe and as an attack of the disease may be short-lived, it is wise to try the least toxic drugs first (Corbett, 1986). However, the majority opinion is that active disease should be treated aggressively (Haslock, 1983).

I. Analgesics and Anti - inflammatory Drugs :

Analgesics serve to reduce pain from joint inflammation, cartilage destruction, or muscle spasm. They may used adjunctively with other medications at any stage, because rheumatoid arthritis is chronic, strong narcotics should be avoided whenever possible (Katz, 1985). Although an NSAID is often given and is sometimes effective, the more logical approach, where there is no inflammation, is often with an analgesic. This reduces the risk of side effects (kantor, 1982).

The mode of action of analgesics is poorly understood but is thought to be both peripherally on the peptide substance-p in the spinal tracts and centrally on the endorphins and enkephalins, it is probable that analgesics act via a competitive action for receptors for these substances on cells (Holt, 1986).

Salicylates and Other NSAIDS :

The use of salicylate drugs in high dosage has largely gone out of fashion because of the high incidence of gastric upset and tinnitus but these drugs are effective and can be tolerated well by some patients (Corbett, 1986).

Ausual starting dose is 0.9 g aspirin four times daily. Salicylates in larger doses are anti-inflammatory and are not just analgesics, patients should be advised that a regular daily dose must be taken for at least two weeks to maintain a blood level of between 20 and 35 mg / deciliter, before deciding on effective (Lightfoot, 1985).

If after a two to four-week trial of salicylates in therapeutic doses in an optimal setting, improvement is insufficient, or if salicylates are not tolerated, another nonsteroidal anti-inflammatory drug should be tried (Lightfoot, 1985).

The NSAIDs have many actions; in addition to the anti-inflammatory they have analgesic and antipyretic

activity. They also affect other metabolic pathways both directly and via their antiprostaglandin and antileukotriene activities. In spite of much research, there is at present no convincing evidence that any of the NSAIDs have an antirheumatic property, that is prevent progressive joint destruction (Holt, 1986). In general, the patient is the best guide to the drug required, and dosage should be adjusted according to response (Gumpel, 1978) care must be taken to use the lowest effective dose of these drugs, particularly in the elderly where side-effects are more common (Wright and Hopkins, 1976).

If patients note no difference if they miss their NSAID, then its efficacy should be questioned. The combination of two drugs, often an analgesic and anti-inflammatory drug, although popular, they should be avoided, there is little evidence of synergism (Holt, 1986). All NSAIDs may cause gastrointestinal upsets, many can cause skin rashes and exacerbate asthma and, particularly in elderly patients, cause problems with water retention. The tendency, because these drugs are highly protein-bound, to increase the effects of anticoagulant treatment can also be aproblem (Corbett, 1986).

Rheumatoid arthritis usually goes into remission during pregnancy (Ungar et al., 1983). NSAIDs should be stopped during pregnancy because absolute safety for the foetus cannot be guaranteed (Corbett, 1985).

A small dose of aspirin is probably safe both for mother and child during pregnancy (Slone, et al., 1976 and Shapiro et al., 1976).

2) Disease Modifying Drugs :

If an adequate trial of aspirin or other NSAID provides insufficient relief, if well-established R.A. has been present for more than oneyear, or if erosions have already occured, disease modifying drugs such as gold, or antimalarial are the next group to be considered (Lightfoot, 1985).

Remittive drugs do not "cure" rheumatoid arthritis they modify the disease activity perhaps to a degree that may simulate a cure. (Shapiro, et al., 1985).

Gold can alter the course of rheumatoid disease (Sigler, et al., 1974) and can even halt radiological damage (Sharp, et al., 1982), though a schedule of 50 mg intramuscularly per week for the first few months has traditionally been used, there is now a trend towards lower doses. (Griffin, et al., 1983). 10 mg weekly regime over a prolonged period, if not effective then larger doses - 20 mg weekly or 50 mg every 2-3 weeks can be given (Holt, 1986). Gold compound may be employed in rheumatoid arthritis patients with felty's or sjogren's syndrome or in R.A. accompanied by preexisting neutropenia or eosinophillia(Mastaglia and Owen, 1981).

Chloroquine is thought to be slightly less powerful and

tends to be used first and in the milder cases, it has an additional benefit that it is effective in both rheumatoid disease and systemic lupus erythematosus. The differentiation between these disorders not always being easy in clinical practice, (Holt, 1986). Antimalarials acts as lysosomal stabilizers and interfere with DNA function, resulting in depressed protein synthesis (Willkin, 1985). Chloroquine can be given safely for many years in doses not exceeding 4 mg/kg lean body weight daily. Hydroxychloroquine also can be given in doses lower than 6 mg / kg/day. Both antimalarial agents have equal therapeutic and toxic effects at these doses. (Mackenxie, 1983). It is strongly bound to melanin, and hence its deposition in retina and skin (Hott, 1986) light exposure accelerates ocular toxicity, and patients should be advised to wear sunglasses when in bright sunlight, to minimize this effect (Lightfoot 1985).

The early retinal lesion is probably reversible, but later lesions are irreversible and may, in fact, be progressive after stopping treatment (Marks, 1982).

Salicylate or other NSAID should be continued in full dosage throughout the period of gold or antimalarial administration (Lightfoot, 1985).

All drug therapy of R.A. is empiric. Most patients requir combined-drug treatment, thus, antimalarial drugs and

gold are often used together in patients with uncontrolled inflammation, especially in those with erosions, (Lightfoot, 1985).

Many rheumatologists now use penicillamine as the next drug of choice in patients unresponsive to treatment with aspirin, gold, and / or antimalarial agents. Some even prefer penicillamine to gold, but the toxicity is ofen serious, even fatal, (Lightfoot, 1985).

D. penicillamine can give results similar to those of gold, (Shoikawa, et al., 1977) and now that it is used in low dosage has a similar incidence of side-effects (Hill, et al., 1979).

As with all the second - line disease remitting drugs some 2-3 months elapse before benefit is apparent (Holt, 1986). and it is usual to discontinue gold therapy, but to continue the other drugs, during the period of penicillamine treatment, because gold may neutralize penicillamine by chelation, (Lighfoot, 1985). Antimalarial agents should not be given in combination with D-penicillamine because they may interfere with its adsorption. Acontrolled trial using both drugs found, The combination inferior to either drug used alone (Bunch, et al., 1984).

At present the therapeutic range has been some 125-750 mg of penicillamine daily. comparison of "low dose" 125-300

mg day and "high dose" 500-600 mg day suggest that lower doses, although apparently less effective, can be continued for longer because of less side effects, and thus in long term. They may be more effective, (Nissila, et al., 1982, and williams et al., 1983). Absorption after oral administration is markedly reduced by food taken at the same time, (Kukovetl, et al., 1983), iron, and antacids also markedly reduce absorption. Thus penicillamine should be given one hour before, or one and a half hours after food, and since it can be given as a single daily dose, at the opposite end of the day to oral iron therapy, (Harkness an Blake, 1982), Large dose of ascrobic acid are thought to inactivate D.Penicillamine and should be avoided, (Mc Carty, et al., 1985).

The toxicities of gold and of penicillamine are similar and have been linked to the presence of the HLA-DR_3 antigen (Lighfoot, 1985), Both drugs may cause rashes although it is sometimes possible cautiously to reintroduce the drug once the rash has gone. Both drugs may cause proteinuria or even the nephrotic syndrome so regular urinalysis must be performed. A potentially more serious side effect with these two drugs is that of bone marrow depression, even aplasia. Some advice a white cell and platelet count before each gold injection. Amonthly blood count is mandatory with D-penicillamine (Corbett, 1986).

Oral gold (Auranofin) :

Auranofin (Ridaura) is an oral form of gold indicated only for proven rheumatoid arthritis (Katz, 1985) Systemic absorption seems to be poor, most of the drug being excreted in the faeces (Holt, 1986). it must be given daily and is less strongly tissue bound, with relatively higher unbound serum level (Lorber, et al., 1983 b).

Auranofin is available as a 3 mg capsule taken twice daily. There will be an option for reducing the dose by half if intolerance is demonstrated. patients may be switched safely from the parenteral to oral form after 1-month overlap of the two (Katz, 1985). Although gastrointestinal side effect such as diarrhea are more frequent with the oral preparation, cutaneous and renal toxicity is substantially less, so that discontinuation of therapy due to adverse reactions has generally been less frequent (Ruddy, 1985).

The clinical evaluation of auranofin continues, but it is probably less effective, but less toxic, than gold sodium aurothiomalate (Ward, et al.,1983).

Lorder et al., (1979) showed an inhibition of both humoral and cell mediated immunity by both oral and intramuscular gold.auranofin differes from sodium aurothiomalate in several respects, including its ability to inhibit lysosomal enzyme release and its lack of potent sulphydryl reactivity (Dieppe, et al., 1985).

No correlation between mean blood levels of gold and clinical response has been noted, but the same absence of correlation has been observed following parenterally administered gold salts (Gottlieb, et al., 1974).

We rarely stop disease modifying drugs in a patient who enters remission and shows no evidence of drug toxicity. The patient should understand that a course of therapy may be of indefinite duration (Shapiro, et al., 1985).

Other drugs with possible anti-rheumatoid activity

Levamisole:

This anti-helminthic agent augments non-specific inflammatory functions by increasing chemotaxis of polymorphonuclear leukocytes and monocytes and their phagocytic functions, (Snyderman and Pike, 1978).

Levamisole has been shown to potentiate the immune response by enhancing lymphoid cell function, (Fauci, 1985). it appears to aid the maturation of T lymphocytes and restores depressed T lymphocytes function. Thus some of its effects are thymomimetic (Holt, 1986), patients treated with levamisole generally do not manifest an increase in the absolute numbers or percentages of lymphocytes. However, reduced numbers of T lymphocytes are restored together with a reduction in the percentage of null cells (non-T, non - B -

cells) (Rosenthal, el al., 1976). Among its many demonstrated actions is an anti-rheumatoid effect. Trials have suggested that, levamisole has a beneficial effect similar to penicillamine (Miller, et al., 1980 and Multicentic study group, 1982).

The major constraint of its use clinically is the incidence and severity of the toxic side effects. These include gastrointestinal disturbances, fatigue, fever and skin rash. However, the most severe and limiting toxic side effect is granulocytopenia, which seems to be disproportionally more frequent in patients with rheumatic diseases. especially these who are HLA-B_{27}- positive (Fauci, 1985). The frequency of side effects may be reduced by using a single weekly dose of about 150 mg, (Dieppe, et al., 1985).

Sulphasalazine :

Mc Conkey, et al., (1980) in an open study showed sulphasalazine to be beneficial in rheumatoid arthritis. More recently, pullar, et al., (1983), in a double-blind comparison with gold and placebo sho-wed both test drugs to be beneficial, though nausea and vomiting proved a problem with sulphasalazine. The possible mode of action of sulphasalazine in alleviating rheumatoid arthritis is speculetive, ligumsky, et al. (1978) showed an anti-inflammatory effect for sulphasalazine, and in particular that it is a prostaglandin synthetase inhibitor.

Thayer et al. (1976) and laursen (1978) demonstrated that sulphasalazine also has an inhibitory effect on lymphocytes.

Disadvantages of sulphasalazine include, reversible azoo-spermia in males and occasional late-onset macrocytic anaemia responsive to folate supplementation. gastrointestinal intolerance is the main practical sideeffect and occurs more frequently in R.A. than in ulcerative colitis it is not always ameliorated by use of enteric-coated tablets or by slow introduction of the drug. The usual maintenance dose is 500 mg. q.d.s. (Dieppe, et al., 1985).

3) Cytotoxic therapy :

The aetiopathogenesis of Rheumatoid arthritis being poorly understood, it is reasonable to try to reduce the activity of both the immune and inflammatory systems, which seem to be overactive, to this end cytotoxic therapy has been used, (Holt, 1986).

Most immunosuppressive drugs are cytotoxic agents which affect the immune system by interfering with proliferation or differentiation of lymphocytes, (Dieppe, et al., 1985), of the drugs presently used. azathioprine, cyclophosphamide, methotrexate, and chlorambucil. The initial aim was to see if they would be steroid sparing and effective in patients unresponsive to gold and penicillamine. With the correct dose

schedule, clinical effect is more rapid than gold or penicillamine - about 4-6 weeks, (Holt, 1986). Azathioprine is used more frequently and is probably safer than chlorambucil, cyclophasphamide and methotrexate (Corbett, 1985). Moens and Brocteur (1965) suggested that the beneficial effect of azathioprine is due to an anti - inflammatory rather than an immunosuppressing action. it has been used in various doses. The conservative schedule, starting with 50 mg day (i.e. 0.75-1 mg / kgm - body weight) and increasing to 100 mg after 1 month if necessary, and then to 150 mg (Holt, 1986). Once started, azathioprine needs to be continued apparently indefinitely, which is worrying (De Silva and Hazleman, 1981), Azathioprine is an antimetabolite affecting purine synthesis, hence, if allopurinol is being used e.g. as a gout prophylactic during lymphoma treatment, the dose of azathioprine must be reduced (Holt, 1986). The relative risk in rheumatic disease is unclear, though leukaemia and reticulum cell sarcoma have been reported in patients with R.A. and SLE who received azathioprine (Dieppe, et al., 1985).

Shapiro et al. (1985) have had very favorable results using oral methotrexate. Methotrexate interferes with folic acid metabolism and thus DNA synthesis in cells, it is therefore most effective where cellular division is most

marked, e.g. in inflammatory states. Antimetabolites of this nature are probably the least likely of the cytotoxic agents to cause neoplasia, (Holt, 1986).

Vomiting, diarrhoea, stomatitis, alopecia, leukopenia thrombocytopenia and marrow aplasia can all occur and may be reduced by administration of folinic acid, infertility is a further problem. Ultra-violet treatment should be avoided in patients on methotrexate because of risk of photosensitivity. intermittent weekly administration is less toxic and less likely to produce liver damage than daily regimes. Adult dosages range from 5 - 40 mg given as a single parenteral dose, or orally as three divided doses separated by 12 hours, each weekend, (Dieppe, et al., 1985).

Most trials suggest that cyclophosphamide is effective in rheumatoid disease, (Currey, et al., 1973, and Townes et al., 1976). its main drawback is its toxicity which is wide ranging. As with many cytotoxic agents, there is the long-term anxiety concerning drug-induced malignant change. Sustained effects on the bone marrow have been demonstrated a decade after treatment, (Thomas, et al., 1983), uroepithelial toxicity, presenting as haemorrhagic cystitis, requires immediate withdrawal since continuation may lead to bladder fibrosis and carcinoma. Amenorrhoea and impaired ovarian function are common and almost all men develop azoospermia which may be permanent. (Dieppe, et al., 1985).

The various trials suggest that 150 mg / day is usually necessary to get benefit, (Holt, 1986).

The combination with prednisolone has been suggested to reduce both the dose of prednisolone necessary and the severity of acute side effects to cyclophosphamide. This type of combination has led to severe viral infections especially of the herpes zoster type (Holt, 1985).

4) Corticosteroids :

The corticosteroids are the most effective anti-inflammatory drugs available, however they are the most toxic in the long run because the adverse effects are often worse than the disease that they are intended to treat. Their routine use is not recommended in rheumatoid arthritis (Katz, 1985) although corticosteroids reduce inflammation, diminish pain, and alleviate stiffness, they do not alter the course of the disease (Ehrlich, 1982).

Corticosteroids may be used in severe disease whilst waiting for gold or D-penicillamine to work. The difficulty here is that of weaning the patient from the steroids once the disease has been modified. A useful alternative could prove to be methylprednisolone pulse therapy which so far seems to be a reasonably safe and effective method of inducing short-term improvement (forster, et al., 1982, and williams, et al., (1982).

Patients with documented seronegative rheumatoid arthritis, may be considered good candidates for low dose corticosteroids, even though drug modifying disease is not presently in the treatment plan. because they are seronegative and retain the potential for spontaneous remission.

Patients who have inadequate control of their disease despite a treatment program that includes The use of multiple anti-inflammatory drugs, including salicylates in therapeutic dosage, NSAD, and drug modifying disease, remain functionally inadequately controlled. Here, Low-dose corticosterioid therapy in a patient at low risk for such therapy may give the "treatment edge" that allows this patient to remain functional, (shapiro, et al., 1985).

The equivalent dose of 5 mg of prednisone is usually tolerated well and provides sufficient relief. The dose of the drugs should always be kept at a minimum and constant attempts at withdrawal are recommended, However, there are those few patients who can not be withdrawn from even 1 milligram of prednisone (Katz, 1985). No dose of corticosteroid is safe, even 5 mg prednisone daily can produce osteopenia (lightfoot, 1985). Because the half life of prednisone is only eight hours. The suppressive effect on the hypothalamic-pituitary axis is minimized and the small dose

given may be additive to the patient's endogenous corticosteroid secretion. treatment with cortico-tropin (ACTH), and fluorinated corticosteroids, such as dexamethasone or triamcinolone, are to be avoided because they have long biologic half lives and are likely to suppress the patient's endogenous corticosteroid output (Lightfoot, 1985).

Local injection of Corticosteroid :

Injection of corticosteroid into a joint is neither specific treatment nor acure for joint inflammation (Hollander, 1985). Local corticosteroids may suppress rheumatoid synovium for weeks to months (Katz, 1985). Aspiration of a joint and instillation of corticosteroids are most useful when only a few joints are involved, particularly when these joints are interfering with the overall progress of the patient (Rudy, 1985). Patients undergoing joint aspiration should be cautioned about excessive use of the joint 24 to 48 hour following the procedure, postinjection infections are rare (Katz, 1985). injection of an area of nerve entrapement may eliminate symptoms for a sufficiently long time as to permit slower acting agents to control the synovitis, thereby eliminating the need for surgical release, (Ruddy, 1985).

Age is no contraindication to this form of therapy,

other than the psychological shock to which such patients may be prone, (Holt, 1986).

Reinjection is done as rarely as possible. The projected result of repeated injections is the production of cartilage destruction and secondary osteoarthrosis. However, if spaced injections i.e. greater than six weeks, are used, This probably does not ocur. (Mc Carty and Hogan,1964). Intraarticular corticosteroid has two distinct sites of action-synovial membrane and cartilage. The first is preferred site and is in a sense protected by its blood supply which will remove corticosteroid. The chondrocytes will however, remain exposed to relatively high concentration of corticosteroid for a long time, (Holt, 1986). All attempts to treat synovitis by local therapy may be flawed since the evidence suggests that the perpetuating influence comes from blood borne cells, particularly lymphocytes (Paulus, et al., 1977).

A much more common, less serious sequel of joint injection has been postinjection flare. Mc Carty and Hogan (1964) demonstrated that this reaction is crystal induced synovitis before the anti-inflammatory effect of the injected crystalline steroid suspension takes over. Local application of ice packs often shorten or even abot this painful reaction fluid should be aspirated and cultured if this reaction persists for more than 24 hours (Hollander, 1985).

III. SURGERY :

An integral part of the management of many patients with rheumatoid arthritis involves orthopedic or plastic surgery (Hall, 1975). Surgical intervention is considered in conjunction with a comprehensive program, most joints are amenable to surgical correction (Katz, 1985).

The indications for surgery in rheumatoid disease are those of intolerable pain and of loss of function which can not be treated medically (Corbett, 1985).

Since the essential pathology of arthritis is synovitis, synovectomy carried out early in the disease, will prevent progressive joint destruction (Mowat, 1978), but the benefits of synovectomy are open to question because synovium regrows within 1 to 2 year post-operatively, However, excision of synovial cysts of tenosynovium is often justified (Katz, 1985).

Total and partial joint replacements have become the keystone of modern joint surgery. The hips, Knees, and small joints of the hands are replaced most commonly .

Arthrodesis is usually reserved for failed arthroplasties or for certain painful unstable joints not amenable to or as alternative to arthroplasty e.g. fusion of the first carpometacarpal joint or ankle (Triple arthrodesis)
(Katz, 1985).

Anterior atlanto-axial subluxation does not require surgical interference until neurologic symptoms are present (Smith, et al., 1972). Fortunately, most patients which cervical spine involvement require only a cervical collar, (Dick and Goodacre, 1985).

Caution must be used in performing surgery on a patient with any of the following problems, a recessed mandible, subluxed or fused cervical spine, or poor ventilation because of rheumatoid lung disease, or restricted chest excursion (Katz, 1985).

Dapsone

History :

Dapsone is a sulfone (4,4-diaminodiphenyl-sulfone). Dapsone was found in 1937 to be 30 times more active and only 15 times as toxic as sulfanilamide when used in streptococcal infections in mice, in 1940s sulfones were found to be effective in suppressing experimental infections with the tubercle bacillus and for rat leprosy, (Mandel and Sande, 1985). but it was not until 1950 that two portuguese physicians, Esteves and Brandau, found this agent effective for dermatitis herpetiformis since that time dapsone has been found to be the drug of choice for both dermatitis herpetiformis and leprosy (Maddin, 1985). Most recently it has been recognized as an effective agent in the treatment of erythema elevatum ditinum (Katz, et al., 1977) as well as the bullous eruptions of S.L.E. (Hal, et al., 1982) it also has some action against malaria and other parasites (Champion, et al., 1986).

The mechanism of action of the dapsone :

Dapsone is bacteriostatic, but not bactericidal. The mechanism of action of the dapsone is probably similar to that of the sulfonamides since both possess approximately the same range of antibacterial activity and both are antagonized by para - aminobezoic acid (Mandell and sande, 1985).

The mechanism whereby dapsone is effective in dermatitis herpetiformis and erythema elevatum diutinum and the bullous skin lesions of S.L.E. are unclear at present. The common denominator of dermatitis herpetiformis and erythema elevatum diutinum is the infiltration of the lesions with neutrophils (Katz, et al., 1977). This has led investigators to put forth a number of hypothesis for mechanisms of effect, including blocking of complement deposition, which removes the chemotactic stimulus to neutrophils (Fauci, 1985).

Absorption, Distribution and Excretion :

Dapsone is available for oral administration and is slowly and nearly completely absorbed from the gastrointestinal tract. Peak concentrations of dapsone are reached in plasma 1 to 3 hours after oral administration, and its half-life ranges from 10 to 50 hours, with a mean of 28 hours, (Mandell and Sande, 1980). Twenty-four hours after an oral dose of 100 mg, plasma concentrations range from 0.4 to 1.2 ug per ml. (Shepard, et al., 1976) about 70% of the drug is bound to plasma protein. The sulfones are distributed throughout the total body water and are present in all tissues. They tend to be retained in skin, muscle, liver and Kidney, with traces of The drug present in these organs up to 3 weeks following cessation of administration. Dapsone is acetylated in the liver, and about 70 to 80 percent of a dose is excreted in the urine (Fauci, 1985).

Untoward Effects :

Side effects with the usual doses are rare (Moschella, 1985). The most common untoward effect is hemolysis of varying degree. This develops in almost every individual treated with 200 to 300 mg. of dapsone per day. Doses of 100 mg. orless in normal healthy persons and 50 mg. orless in healthy individuals with a glucose -6- phosphate dehydrogenase deficiency do not cause hemolysis (De Gown, 1967). Methemoglobinemia is also common and is responsible for the bluish lips etc., so common in patients on this drug (Champion, et al., 1986).

Other side effects include anorexia, nausea, and Vomiting Rarely, headache, nervousness, insomnia and reversible peripheral neuropathy (Fauci, 1985) drug fever, hematuria, pruritus, psychosis, and avariety of skin rashes have been reported (Rapoport and Guss, 1972).

The development of the diaminodiphenyl sulfone syndrome, a hypersensitivity reaction (pseudoinfectious mononucleosis syndrome), fortunately is rare (Maddin, 1985).

Dosage :

The recommended dosage schedule for dapsone, initiate

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The recommended dosage schedule for dapsone, initiate

although effective, dapsone is not as useful as chloroquine.

Kelly and Griffiths (1981) have also confirmed the efficacy of dapsone, but found much greater falls in haemoglobin. Grindulis and Mc Conkey (1982) found that haemoglobin level fell by one gram in the first six week but thereafter tended to rise, probably as disease activity lessened, so they concluded that significant anaemia is probably not a common serious side effect providing that patients start with areasonable haemoglobin level and providing they have normal glucose -6- phosphate dehydrogenase (G6PD) level, and so in patients genetically dificient in G6PD. The risk of profound anaemia is very great, this deficiency is mainly encountered in peoples of Mediterranean and chinese origin.

All studies agree that a mild haemolytic anaemia and agranulocytosis can occur. The usual dose would be 100 mg per day (Holt, 1986).

PATIENTS AND METHODS

Patients:

43 patients suffering from rheumatoid arthritis were selected from the outpatient clinic of the Rheumatology and Rehabilitation Department at Benha University Hospitals. They were 6 males and 37 females with age ranging from 32 to 60 years (mean age 46.13 + 7.55 years old).

The selected patients fulfilled the American Rheumatism Association criteria for definite or classical rheumatoid arthritis (Ropes et al., 1959). An assessment of disease activity corresponding to functional class I, II or III (Steinbrocker et al., 1949).

Cases of Rieter's disease, gout, colitic arthropathy, ankylosing spondylitis and probable cases were excluded.

Patients were also excluded, if there was a history or presence of one of the following conditions:

* Hepatic or renal disease, cardiac failure, known or suspected peptic ulcer, diabetes mellitus, blood diseases, moderate and severe anaemia, known or suspected pregnancy and patients in whom acetyl salicylic acid or other prostaglandin synthetase inhibitors are known to precipitate an attack of

asthma or urticaria.

* Gold, penicillamine or other suppressive agents were not administered for at least 3 months before the start of the study. Patients on corticosteroids were admitted. The dose of corticosteroid or any orally administered nonsteroidal anti-inflammatory drugs had to be constant during the last month before entry into the trial.

Diagnostic Criteria For Rheumatoid Arthritis:

I. American Rheumatism Association Criteria (Ropes et al., 1959):

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint.
3. Swelling of one joint, representing soft tissue thickening or fluid.
4. Swelling of at least one other joint (soft tissue or fluid) with an interval free of symptoms no-longer than 3 months.
5. Symmetrical joint swelling (Simultaneous involvement of the same joint, right and left).
6. Subcutaneous nodules over bony prominences, extensor

surfaces or near joints.

7. X-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joint and not just, degenerative changes) - degenerative changes do not exclude rheumatoid arthritis.
8. Positive test for rheumatoid factor in serum.
9. Synovial fluid, a poor mucin clot formation on adding synovial fluid to dilute acetic acid.
10. Characteristic histological changes in synovial membrane with three or more of the following:
    - Marked villous hypertrophy.
    - Proliferation of superficial synovial cells often with palisading.
    - Marked infiltration of chronic inflammatory cells (Lymphocytes or plasma cells) with tendency to form lymphoid nodules.
    - Deposition of compact fibrin either on surface or interstitially.
    - Foci of cell necrosis.
11. Characteristic histological changes in rheumatoid nodules showing granulomatous foci with central zones of cell

necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

For three different degree (categories) of certainty of diagnosis, different numbers of criteria must be met:

* Classic rheumatoid arthritis: 7 criteria needed.
* Definite rheumatoid arthritis: 5 criteria needed.
* Probable rheumatoid arthritis: 3 criteria needed. to meet criteria 1 to 5, symptoms or signs must be present for at least six weeks.

Exclusions:

1. The typical rash of disseminated lupus erythematosus.
2. High concentration of lupus erythematosus cells.
3. Histologic evidence of periarteritis nodosa.
4. Weakness of neck, trunk, and pharyngeal muscles or persistent muscle swelling or dermatomyositis.
5. Definite scleroderma.
6. Clinical picture characteristic of rheumatic fever.
7. Clinical picture characteristic of gouty arthritis.
8. Tophi.
9. Clinical picture characteristic of acute infectious

arthritis.

10. Tubercle bacilli in the joints or histologic evidence of joint tuberculosis.
11. Clinical picture characteristic of Reiter's syndrome.
12. Clinical picture characteristic of shoulder hand syndrome.
13. Clinical picture characteristic of hypertrophic pulmonary osteoarthropathy.
14. Clinical picture characteristic of neuroarthropathy.
15. Homogentisic acid in the urine detectable grossly with alkalinization.
16. Histologic evidence of sarcoid or positive kveim test.
17. Multiple myeloma as evidenced by marked increase in plasma cells in the bone marrow, or Bence-Jones protein in the urine.
18. Characteristic skin lesions of erythema nodosum.
19. Leukemia or lymphoma with characteristic cells in peripheral blood, bone marrow or tissues.
20. Agammaglobulinemia.

The weakness of this criteria is in application to the "probable" class of diagnosis, when only 3 criteria are necessary, the firmness of the diagnosis varies considerably,

depending on which 3 are picked, for instance, a patient with morning stiffness and a single painful swollen joint would meet criteria for "probable" rheumatoid arthritis (Harris, 1985).

II. The 1987 Revised American Rheumatism Association Criteria for Rheumatoid Arthritis (Arnett et al., 1988):

1. Morning stiffness: in and around joints at least 1 hour.
2. Soft tissue joint swelling observed by physician at least 3/14 joint groups. (Rtor Lt.: MCP, PIP, Wrist, Elbow, Knee Ankle, MTP).
3. Soft tissue joint swelling in a hand joint. (MCP, PIP. or Wrist).
4. Symmetrical swelling of one joint area: in 2 above.
5. Rehumatoid nodules.
6. Rheumatoid factor by method positive in < 5% normal population.
7. Radiograph changes on wrist/hands: erosions or juxta-articular osteoporosis.

RA = 4/7 criteris.

In brief, in the new version there is only one degree of diagnostic certainty of Rheumatoid arthritis, requiring four

of the seven listed criteria.

Drawbacks of the New Criteria:

1. The development of an alternative formulations may be a source of confusion.
2. The patient studied to formulate these criteria were current attenders with established disease (mean duration 7.7 years) where diagnostic criteria are of greatest utility in early disease. Thus the sensitivity of these criteria at diagnosis remains unknown.
3. There are no exclusions, as with the original criteria.
4. The exclusion of the shoulder from the list of involved joints might be a surprise to many, as shoulder involvement is not a rare event in R.A.

Methods:

All patients were subjected to the following:

I. A Full History of the present illness was taken from each patient, starting by filling a proforma that included:

A) Personal History:

Name Age Sex

Address occupation.

Marital status Special Habits.

B) Complaint:

Taken in the patient's own words.

C) Present History:

- Date of onset.
- Mode of onset, acute, rapid, insidious
- Duration and course of the disease.
- Sequence of joints involvement.
- Pattern and symmetry of the joints involved.

* Morning stiffness Duration
* Pain: - Type - severity - Timing
  - Localisation- What increased and what decreased.
* Swelling.
* Functional capacity of the patient according to steinbrocker grading (Steinbrocker et al., 1949).
* Presence or absence of Raynaud's phenomenon.
* Dryness of eyes.

  Dryness of mouth.

* Chest symptoms.

* Gastrointestinal sysmptoms.

* Cardiovascular symptoms.

* Neurological symptoms.

* Urinary symptoms.

* Menstruation troubles.

DD Past History of disease.

ED Family History: of similar conditions in the family.

FD Previous Therapy:

* Medical

Kind	Dose	Duration	Effective-ness	Side effects

* Physical Therapy.

  Response.

* Surgical procedures :

  Response.

* Local injections.

  Response.

II General Examination :

- general appearance.
- weight - height.
- Temperature - pulse - Blood pressure.
- Examination of eyes and mouth. for evidence of Conjunctivitis, irritis or mouth ulcerations.
- Examination of the skin for subcutaneous swellings, (subcutaneous nodules or subcutaneous Tophi) and for skin lesions suggestive of collagen diseases.

- Examination of lymph glands.
- Chest examination.
- Cardiovascular examination.
- Abdominal examination.
- Neurological examination including motor power, sensations, superficial reflexes and deep reflexes.

III Locomotor system examination :

- Hand examination :
    * Vascular lesions.

* Nails.
* Distal inter - phalangeal joints.
* Proximal inter-phalangeal joints.
* Meta - Carpophalangeal joints.
* Grip strength.

- Wrist joints.
- Elbow joints.
- Shoulder joints.
- Acromio - clavicular joints.
- Sterno - Clavicular joints.
- Temporo - mandibular joints.
- Cervical spine.
- Dorsal spine.
- Lumbar spine.
- Sacro - iliac joints.
- Hip joints.
- Knee joints.
- Ankle joints.
- Foot examination.
    * vascular lesions.
    * Nails.
    * proximal inter - phalangeal joints.

* Metatarso - phalangeal joints.

* Mid-tarsal joints.

* Subtaloid joints.

- Examination of posture and gait.

Each of the above joints will be examined according to the following:

(1) inspection :

- The overlying skin.
- Muscle wasting.
- Deformity.
- Swelling.
- Heberden's nodes are locked for over the distal interphalangeal joints.

(2) Palpation :

- Temperature:
- Tenderness to pressure or passive movement.
- Swelling: synovial and bony swelling were detected by careful palpaion and whenever accessible e.g: Th knee effussion was detected by cross fluctuation,

ballotment of the patella or lateral displacement and ballooning.

- Palpation of the bony Components of the joints.

(3) movements :

- Both active and passive movements are tested.
- Measurement of the range of motion of each joint is carried out in Conjunction with observations regarding;

- abnormal movements (instability).
- pain on movement.
- Crepitus.
- protective muscle spasm.

The hitory included special attention to:

1. Duration of morning stiffness in minutes (McCarty, 1979).

2. Onset of fatigue in afternoon orevening in hours (Mccarty, 1979).

3. The functional capacity of the patient which was graded into four grades according to Steinbrocker et a. (1949).

Grade I: The patient can perform all normal activities.

Grade II: Normal activities, but performed with handicap of pain or limited joint motion.

Grade III: Limited activities of daily living or occupational activities.

Grade IV: Patient is confined to wheel chair or bedridden.

Local joint examination included special attention to:

1. Counting the number of the limb joint (taking the hands and feet as single units) that were painful when put through the maximum possible active range.

2. Counting the number of swollen joints (Buchannan and Tugwell, 1985).

3. **Tenderness:** was elicited by firm manual pressure on the joint margin or by passive movement and the Ritchie Articular Index (1968) was scored according.

To the grades: 0 = patient has no tenderness, 1 = patient complains of pain, 2 = patient complains of pain and winces, 3 = patient complains of pain, winces and withdraws the limb.

Tenderness of the cervical spine, hip joints and talocalcaneal and midtarsal joints is elicited by passive movement. Some joints are treated as single units:

Temporomandibular, sternoclavicular, acromioclavicular, and metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints of the hands. The total sum of the Ritchie articular index is 78.

The intraobserver error with the Ritchie index when performed within 30 minutes is highly acceptable (mean differences between 1 and 2 units). The interobserver error is high, and it has been calculated that differences less than 20 between two observers in an individual patient can not be interpreted as significant. This finding once again emphasizes the need for a single observer to make the measurement in a clinical therapeutic trial (Ritchie et al., 1968).

4. Joint circumference of the proximal interphalangeal joints was accurately measured by the spring gauge (Boardman and Hart, 1967).

5. Grip strength measurement:

Using a modified sphygmomanometer cuff inflated up to 20 mmHg (McCarty, 1979). The patient is asked to squeeze the cuff as hard as possible, keeping the arm unsupported, and the height of the mercury column is observed, the highest of three readings for each hand is recorded.

III. Laboratory Investigations:

1. Urine analysis for protein and sugar.

2. Blood picture including, Haemoglobin percentage, Red cell count, and white cell count both total and differential (Dacie and Lewis, 1975).

3. Platelet count.

4. Erythrocyte sedimentation rate by Westergren, 1926 method.

5. C-reactive Protein (CRP).

By single radial immunodiffusion (Mancini et al., 1965) using L C-partigen of Behring institute. Fill wells 1 to 3 with 20 ul each of the standard dilutions 1:1, 1:2 and 1:4 (3 different concentrations) then put the samples (each 20 UL) in wells 4 to 12, measure the precipitation rings after 2-3 days. Using linear graph paper. Plot the squares of the diameters of the precipitate rings obtained with the standard dilutions as a function of the concentration. The graph thus obtained will normally be a straight line from which the concentration of CRP in the samples examined can be read off directly.

6. Measurement of serum rheumatoid factor by latex-slide agglutination and testing of dilution series (Watson, 1965).

In screening test: marked agglutination indicated the presence of rheumatoid factor (RF); serum samples not reacting with latex-RF reagent did not contain any rheumatoid factors, or had concentrations less than 20 IU/ml. for semi-quantitative determination: a dilution series of the patient's serum with 0.4% saline solution was prepared and tested with the latex. RF reagent when agglutination took place in the serum dilutions of 1 + 5, 1 + 10, 1 + 20, 1 + 30 1 + 40, it indicated that the RF was present in a concentration of about 20 IU/ml, 40 IU/ml, 80 IU/ml, 120 IU/ml, and 160 IU/ml respectively.

7. Liver function test:

1. Determination of Aminotransferases (Tietz, 1970):

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Principle:

- Oxoglutarate + L. aspartate $\xrightleftharpoons{AST}$ L. glutamate + Oxalacetate.
- Oxoglutarate + L. alanine $\xrightleftharpoons{ALT}$ L-glutamate + Pyruvate.

The amount of oxalacetate or pyruvate produced has been estimated by forming 2, 4-dinitrophenylhydrazone. The colour

of which in alkaline solution is red.

II. Determination of Alkaline Phosphatase in Serum (King and Armstrong method, 1934).

The substrate disodium phenyl phosphate is hydrolyzed by the phosphatase enzyme with liberation of phenol and formation of sodium phosphate at optimum pH (pH 10) for 15 minutes. The amount of phenol liberated by hydrolysis forms a blue colour with folin and Ciocalteau's phenol reagent (which also precipitates proteins) in presence of sodium carbonate 25%, which can be estimated colorimetrically.

N.B. The K.A. unit is converted to IU/Liter by multiplying the result by 7.09.

8. Renal Function Test:

I. Determination of Serum Creatinine (Brod and Sirota, 1948):

The method depends on the production of a red colour with an alkaline picrate solution (Jaffe reaction).

$$\text{Serum creatinine (U mol/L)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 200$$

Determination of Blood Urea:

The urease method using the Berthelot reaction (Martineck, 1964).

Principle: The amonia formed from urease action reacts with phenol in the presence of hypochlorite to form an indophenol which with alkali gives a blue coloured compound. Nitroprusside acts as a catalyst, increasing the rate of reaction, the intensity of the colour obtained and its reproducibility.

$$\text{Blood Urea (mmol/L)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 20$$

Drug Administration:

* Medications were given in a randomised double blind manner for 6 months duration patients were randomly allocated dapsone or placebo and stratified for age, sex and corticosteroid consumption.

* 22 patients received dapsone and 21 placebo. They were supplied in coded, unidentifiable tablets for oral administration.

* Dapsone was administered in a dose of 50 mg / day for a week and 100 mg daily there after.

* Placebo was administered as tablets, identical to dapsone tablets.

* Any concomitant therapy, especially.

Anti-inflammatory analgesics was noted during the trial, and special instruction for patients to maintain their pretrial dose of anti-inflammatory analgesics.

* Patients were instructed to report immediately to the hospital in cases of exacerbation of symptoms, untoward side effects or even low tolerability, otherwise flow up weekly during the first month, and monthly during the next five months.

Follow-up Consultation:

* Date of consultation.

* Main Complaint.

* Weight Temp. Pulse B.P.

* Clinical assessment.

Parameter	Result.
1. Duration of morning stiffness	
2. Joint count assessment.	

- Number of painful joints
- Number of swollen joints
- Joint tenderness (A.I)

3. Circumference of PIP. joints.

4. Grip strength Rt.
Lt.

6. General overall condition of patient.

General overall condition of patient:

good = 1, Satisfactory = 2, Poor = 3

* Other concommitant medication:

Drug	Dosage	Reason for administration

Laboratory assessment:

Parameter	Results	Normal range	Date taken
* HB			
* R.B.Cs.			
* W.B.C.			
differntial			

- Neutrophil
- Lymphocyte
- Basophil
- Easinophil
- Monocyte

* E.S.R.

* C-Reactive protein

* Rheum, factor

Liver Function

- SGPT (ALT)
- SGOT. (AST)
- Alkaline phosphatase (ALP)

Renal function
- Blood urea.
- Serum creatinine

Urine analysis

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* Side effects of treatment:

If present state severity, mild, moderate or severe.

List side effects

(----------)

(----------)

(----------)

* Withdrawal from study:

Withdram from trial: Date / / Reason .....

Patients were requested to present for follow up visits on the same time of the day.

Evaluation was done by the physician who is unaware which type of drug regimen the patient was receiving in order to avoid anticipation of results, after 6 months clinical and laboratory study evaluations were adopted.

Statistical Analysis:

The statistics of this work was done on the IBM personal Computur. using the microstate statistical programme (Ecosoft - Inc. 1985)

RESULTS

43 rheumatoid arthritis patients were carefully selected according to ARA criteria. They had classical or definite R.A. They were 6 males and 37 females. Their age ranged from 32 to 60 years old with a mean value of 46.13 ± 7.55 years. The duration of the disease ranged from 2 to 12 years, with a mean value of 5.046 ± 2.36 years.

Figure 1 shows the distribution of rheumatoid cases according to sex.

Figure 2 shows the incidence of rheumatoid arthritis according to the age. It had been observed that the majority of patients had their onset in the 4th and 5th decades of age as (79.1%) had their onset in these two decades. On the other hand the onset was less frequent in the 3rd and 6th decades as incidence was 11.6% and 9.3% respectively.

The earliest age of onset in the present work was 28 years, while the eldest was 54 years.

Table (2) shows the distribution of the affected joints. It was noticed that the hand and wrist joints were more frequently involved than the other joints. As the frequency

of involvement was 93% hand, 88% wrist joints. While the cervical, temperomandibular and hip joints were less frequently involved as the frequency of involvement was 9%, 12% and 12%, respectively.

Table (1) summarises patient characteristics at the start of the trial. There was no significant difference of demographic data between the two groups and also there was no significant difference of the clinical and laboratory variables measured between the two groups **(Tables 13, 14, 15, 16, 17).**

Withdrawals and Drop-outs:

During the 6-month study period 3 patients were withdrawn, 2 from the dapsone group and 1 from the placebo group.

In the dapsone group one patient was withdrawn because of side effects. He felt general unwell, he developed a characteristic pallor, haemoglobin concentration felt by 2 gm/100 ml. and he stoped dapsone after 3 weeks from the start of the trial, and the other patient dropped out owing to treatment inefficacy, after 2 months from the trial.

In the placebo group, one patient was dropped out

because of treatment inefficacy after 3 months from the trial.

Results of Dapsone Therapy on The Clinical Data:

Table (3) shows the effects of dapsone therapy. On certain clinical parameters, in rheumatoid arthritis, with significant decrease in the duration of the morning stiffness from an average mean of 68.25 ± 25.97 min. for every patient before medication to 28.5 ± 8.75 min. following dapsone administration.

Dapsone produced a decrease in the number of painful joints from an average mean of 11.5 ± 1.88 joints before treatment to 4.5 ± 1.24 joints at the end of dapsone therapy. Also dapsone produced a decrease in the number of swollen joints. From a mean of 6.75 ± 1.62 joints, before medication to a mean of 2.3 ± 1.13 joints after Dapsone therapy. Similarly joint tenderness was significantly decreased as measured by Ritchie articular index from the mean value of 32.95 ± 3.98 before treatment. To a mean value of 13.85 ± 3.07 following dapsone therapy (Fig., 3).

Dapsone produced a non significant increase in the grip

strength from an average mean of 59 ± 13.33mmHg for each patient before medication to an average mean of 64.25 ± 11.5 mmHg. at the end of the dapsone therapy.

Dapsone produced a significant reduction in the circumference of proximal interphalangeal joints (total of 10 joints), from the average mean of 579.8 ± 11.21 mm. for each patient before therapy to the average mean of 563.8 ± 12.68 mm. following dapsone therapy.

Laboratories Studies in Rheumatoid Arthritis Before and After Dapsone Therapy:

Table (4) illustrates the effects of Dapsone therapy on Haemoglobin concentration, total white cell count and differential white cell count. In this group Haemoglobin concentration was significant decrease from 11.14 ± 0.86 gm/100 ml before therapy to 10.29 ± 0.69 gm/100 ml following Dapsone treatment.

The white cell count showed insignificant changes as it was insignificantly increased from 6790 ± 1466 cell/ml before to 6965 ± 1467 cell/ml after dapsone treatment. On the other hand the changes induced by dapsone treatment on the differential white cell count was insignificant as neutrophil

percentage changed from 60.7 ± 7.30 to 60.3 ± 6.50, lymphocytes percentage from 34.3 ± 6.24 to 34.6 ± 5.95. Esinophil changed from 2.4 ± 0.88 to 2.4 ± o.94. Basophil changed from 0.05 ± 0.22 to 0.15 ± 0.37 and also monocytes changed from 3.05 ± 1.099 to 3.15 ± 1.089 following dapsone therapy.

Table (5) illustrates the effects of Dapsone treatment on Erythrocyte sedimentation Rate (E.S.R.), C-Reactive protein (CRP) and Rheumatoid factor concentration (Latex Titre). In this group the mean value of sedimentation rate using westergren method was significantly decreased from 49.25 ± 6.40 mm/hr before medication to 26.7 ± 5.64 mm/hr following dapsone therapy, and also, the mean value of C-reactive protein (CRP) using immunodiffusion method was significantly decreased from 5.11 ± 1.01 mg/dl before treatment to 2.98 ± 0.64 mg/dl after Dapsone treatment. On the other hand Rheumatoid factor concentration determined by semi-quantitative method using the latex-RF reagent and dilution series of the patient's serum showed insignificant changes from 104 ± 57.16 IU/ml before to 100 ± 49.42 IU/ml after Dapsone administration.

Table (6) (Fig. 4) shows the effects of Dapsone therapy

on alanine aminotransferase "ALT". Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The mean value of alanine aminotransferase (ALT) was insignificantly increased from 9.15 ± 2.54 U/L before, to 9.35 ± 1.93 U/L after Dapsone therapy. As regard aspartate aminotransferase (AST) its value was insignificantly increased from 10.05 ± 1.88 U/L to 10.35 ± 1.81 U/L following dapsone therapy. Moreover the serum alkaline phosphatase (ALP) showed insignificant changes as it increased from 55.9 ± 13.49 I.U./L. before to 56.8 ± 12.56 IU/L after dapsone administration.

Table (7) illustrate the effects of dapsone treatment on serum creatinine and blood urea. The mean value of serum creatinine was insignificantly increased from 84.5 ± 10.61 ummol/L before to 86.05 ± 9.21 ummol/L after dapsone therapy. Similarly blood urea was insignificantly changed from 4.69 ± 0.70 mmol/L. before to 4.75 ± 0.54 mmol/L after dapsone administration.

Results of Placebo Therapy on the Clinical Data:

Table (8) illustrates the effects of placebo therapy on certain clinical parameters in rheumatoid arthritis patients.

With non significant decrease in the duration of the morning stiffness from an average mean of 69.75 ± 26.33 min. before medication to an average mean of 64.25 ± 23.96 min. after placebo treatment.

Placebo produced a non significant decrease in the number of painful joints from an average mean of 10.75 ± 2.14 joints before treatment to 10.25 ± 1.33 joints after placebo therapy. Also placebo produced a non significant decrease in the number of swollen joints from an average mean of 6.45 ± 1.6 joints for every patient before medication to an average mean of 5.45 ± 1.53 joints at the end of placebo therapy, on the other hand joint tenderness as measured by Ritchie articular index was nonsignificant decreased from a mean value of 31.35 ± 3.52 before treatment to 30.35 ± 2.47 after placebo treatment (Fig., 5).

Also placebo produced no change in the mean value of grip strength as the mean value of grip strength for every patient before and after placebo was 60 mmHg.

Placebo produced a non significant decrease in the circumference of proximal interphalangeal joints (Total of 10 joints) from the average mean of 582.4 ± 11.9 mm. for every patient before therapy to an average mean of 581.55 ± 9.41 mm

following placebo therapy.

Laboratories Studies in Rheumatoid Arthritis Before and After Placebo Therapy:

Table (9) shows the effects of placebo therapy on Haemoglobin concentration, total and differential white cell count in rheumatoid arthritis patients.

The mean value of haemoglobin concentration was insignificantly changed from 11.01 ± 0.80 gm/100ml before therapy to 11.06 ± 0.77 gm/100ml following placebo therapy.

The white cell count showed also insignificant changes. As it was insignificantly changed from 6230 ± 1.082 cell/ml. to 6250 ± 0.907 cell/ml after placebo therapy. Moreover the changes induced by placebo therapy on the differential white cell count was also insignificant. As neutrophil percentage changed from 59.95 ± 5.18 before therapy to 59.65 ± 4.31 after placebo treatment, lymphocytes changed from 36.05 ± 5.26 to 35.5 ± 3.94. Eosinophil changed from 1.95 ± 0.68 to 2.1 ± 0.64. Basophil changed from 0.1 ± 0.30 to 0.3 ± 0.47, and there was no change in the mean value of the percentage of monocyte, before and after placebo therapy.

Table (10) shows the effects of placebo on erythrocyte

sedimentation rate, C-reactive protein and rheumatoid factor concentration (latex titre). The mean value of sedimentation rate using westergren method showed insignificant decrease from 50.2 ± 8.50 mm/hr before therapy to 48.65 ± 6.53 mm/hr following placebo treatment.

Also the mean value of C-reactive protein using immunodiffusion method was insignificantly changed from 4.85 ± 1.08 mg/dl before treatment to 4.84 ± 0.85 mg/dl after placebo treatment. On the other hand rheumatoid factor concentration determined by semi-quantitative method using the latex-RF reagent and dilution series of the patient's serum showed insignificant changes from 100 ± 54.28 IU/ml before medication to 105 ± 52.26 after placebo administration.

Table (11) [Fig., 6) shows the effects of placebo therapy on alanine aminotransferase (ALT), aspartate amino-transferase (AST) and alkaline phosphatase (ALP) in rheumatoid arthritis patients.

The mean value of alanine aminotransferase (ALT) was insignificantly increased from 9.3 ± 207 U/L before therapy to 9.45 ± 1.57 U/L after placebo therapy.

As regard aspartate aminotransferase (AST) its value was

insignificantly increased from 9.08 ± 1.87 U/L to 9.55 ± 1.39 U/L following placebo therapy.

Moreover the serum alkaline phosphatase (ALP) showed insignificant changes as it increased from 56.3 ± 11.35 U/L before to 56.35 ± 9.04 U/L after placebo administration.

TAble (12) shows the effects of placebo therapy on serum creatinine and blood urea in rheumatoid arthritis patients.

The mean value of serum creatinine was insignificantly changed from 83.75 ± 8.71 ummol/L before therapy to 83 ± 5.71 Ummol/L after placebo therapy. Similarly blood urea was insignificantly changed from 4.7 ± 0.72 mmol/L before to 4.67 + 0.38 mmol/L after placebo administration.

Comparison of Therapeutic Effects of Dapsone and Placebo on Clinical Data:

Tables (3, 8, 13) illustrates the effects of the two therapeutic lines on certain clinical parameters of rheumatoid arthritis.

* The duration of morning stiffness in the dapsone group showed a highly significant decrease ($P < 0.001$) when

compared with the placebo group (Fig., 7).

* Dapsone produced a highly significant reduction (P < 0.001) in the number of paniful joints when compared to the placebo therapy.

* The number of swollen joints was highly significant decreased (P < 0.001) following dapsone therapy when compared to the placebo therapy.

* The value of Ritchie articular index for the group receiving dapsone was highly significantly decreased (P < 0.001) when compared with the group receiving placebo (Fig.,8)

* Dapsone produced a nonsignificant increase in the grip strength (P > 0.05) when compared to the placebo therapy (Fig. 9).

* Dapsone produced a highly significant reduction (P < 0.001) in the circumference of P.I.P.Js when compared to the placebo therapy.

Comparison of therapeutic Effects of Dapsone and Placebo on laboratory Findings:

Tables (4, 9, 14) shows the effects of the two

therapeutic lines on Haemoglobin concentration, total and differential white cell count.

* The haemoglobin concentration was highly significant decreased (< 0.001) in the dapsone group when compared to the placebo group.

* The white cell count showed insignificant increase (P > 0.05) following dapsone therapy when compared to placebo theray.

* As regards differential white cell count, there was insignificant changes (P > 0.05) following dapsone therapy when compared to the placebo therapy.

Tables (5, 10, 15) shows the effects of the two therapeutic lines on E.S.R., C.R.P., and rheumatoid factor concentration (latex titre).

* ESR was highly significant decreased (P < 0.001) following dapsone therapy when compared to placebo therapy **(Fig. 10).**

* CRP was highly significant decrease (P < 0.001) following dapsone therapy when compared to placebo therapy **(Fig., 11).**

* There was insignificant change (P > 0.05) in latex titre following dapsone therapy when compared to placebo therapy.

Tables (6, 11, 16) shows the effects of the two therapeutic lines on ALT, AST, and ALP.

* All changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were insignificant (P > 0.05) following dapsone therapy when compared to placebo therapy (Fig., 12).

Tables (7, 12, 17) shows the effects of the two therapeutic lines on serum creatinine and blood urea in rheumatoid arthritis patients.

The changes in serum creatinine and blood urea were insignificant (P > 0.05) following dapsone therapy when compared to placebo therapy (Fig , 13 , 14)

Side Effects:

Table (18) showes the side effects commonly encountered in this study.

At The 4th Week:

* 2 patients in the dapsone group and 4 patients in the placebo group complained of Rash and pruritis.

* 6 patients of the dapsone group and 6 patients of the placebo group complained of gastrointestinal upset, Nausea and dyspepsia.

* 7 patients of the dapsone group and 4 patients of the placebo group complained of Dysnea, and palpitation.

* 7 patients of the dapsone group and 6 patients of the placebo group complained of headache and dizzness.

At The End of The Trial:

* 3 Patients of the placebo group complained of Rash and pruritis.

* 1 patient in the dapsone group and 3 patients of the placebo group complained of gastrointestinal upset neusea and dyspepsia.

* 1 patient in the dapsone group and 2 patients of the placebo group complained of dysnea and palpitation.

* 2 patients in the placebo group complained of headache and dizzness.

* Although specifically instructed for patients to maintain their pretrial dose of anti-inflammatory analgesics, 1 patient in the dapsone group stopped analgesics at week 20, and 3 patients in dapsone group took less of the supplemental analgesics from the week 11 and thereafter, but none did in the placebo group.

TABLE (1)

Characteristics of the rheumatoid arthritis patients at the start of the Trial.

Characteristics	Dapsone group	Placebo group
Number of patients	22	21
Age (years)	46.59 ± 7.5	45.67 ± 7.76
Sex / F / M	19 / 3	18 / 3
Disease duration / years	5.045 ± 2.49	5.04 ± 2.2
Patients on Corticosteroids	4	4

TABLE (2)

The distribution of the affected joints .

Joint	% of involvement
Hand joints (PIP & MCP)	93 %
Wrist	88 %
Elbow	67 %
Shoulder	53 %
Hip	12 %
Knee	74 %
Ankle	67 %
Foot joints	56 %
.te mpro - mandibular	12 %
Sterno - clavicular	20 %
Cervical	9 %

PIP : Proximal interphalangeal .

MCP : Meta Carpo - Phalangeal .

TABLE (3)

The effects of Dapsone Therapy on certain clinical parameters expressed as range, mean, SD before and after Therapy

		Morning Stiffness (min)	Number of Painful joints	Number of Swollen joints	Ritchie index	Grip strength (mm Hg)	PIP Circumference (mm. total of 10 joints)
Before Dapsone No. 20	Range	120 to 45	16 to 8	10 to 4	42 to 27	80 to 35	600 to 560
	Mean	68.25	11.50	6.75	32.95	59	579.80
	SD	25.97	1.88	1.62	3.98	13.33	11.21
After Dapsone No. 20	Range	45 to 15	7 to 3	4 to 0	20 to 8	90 to 40	590 to 540
	Mean	28.50	4.50	2.30	13.85	64.25	563.80
	SD	8.75	1.24	1.13	3.07	11.50	12.68
P		< 0.001	< 0.001	< 0.001	< 0.001	> 0.05	< 0.001

* Non Significant P > 0.05

TABLE (4)

The effects of Dapsone Therapy on HB, Total and differential white cell count. in rheumatoid A. patients expressed as range, mean and standard deviation (S.D).

		Haemoglobin % gm / 100 ml	Total white cell Count.		differential white cell count			
				Neutrophil %	Lymphocyte %	Eosinophil %	Basophil %	Monocyte %
Before Dapsone No. 20	Range	13.2 to 10	10 to 5	73 to 42	50 to 24	4 to 1	1 to 0	5 to 1
	Mean	11.14	6.790	60.7	34.30	2.40	0.05	3.05
	SD	0.86	1.466	7.39	6.24	0.88	0.22	1.099
After Dapsone No. 20	Range	12 to 9.2	9.8 to 5.4	70 to 42	50 to 25	5 to 1	1 to 0	5 to 2
	Mean	10.29	6.965	60.30	34.60	2.40	0.15	3.15
	SD	0.69	1.467	6.95	5.95	0.94	0.37	1.089
P		< 0.001	> 0.05*	> 0.05*	> 0.05*	0*	> 0.05*	> 0.05*

* Non significant P > 0.05

TABLE (5)

The effects of Dapsone Therapy on E.S.R. & C.R.P. & R.F. (Latex Titre) expressed as range, Mean and S.D. before and after Therapy in rheumatoid arthritis patients .

		Erythrocyte sedimentation rate mm / hr	C - reactive protein mg / dL	Rheumatoid factor (Latex Titre) IU / ml
Before Dapsone No. 20	Range	92 to 38	6.5 to 3.5	160 to 0
	Mean	49.25	5.11	104
	SD	6.40	1.01	57.16
After Dapsone No. 20	Range	40 to 20	4 to 2.2	160 to 0
	Mean	26.70	2.98	100
	SD	5.64	0.64	49.42
P		< 0.001	<0.001	> 0.05*

* Non Significant P > 0.05

Table (6)

The effects of Dapsone therapy on alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), in rheumatoid arthritis patients expressed as Range, Mean and SD .

		ALT U / L	AST U /L	ALP U / L
Before Dapsone No. 20	Range	14 to 5	12.4 to 7	90 to 30
	Mean	9.15	10.05	55.9
	SD	2.53	1.87	13.49
After Dapsone No. 20	Range	15 to7	12.6 to 8	100 to 28
	Mean	9.35	10.35	56.80
	SD	1.92	1.81	12.56
P		> 0.05	> 0.05*	> 0.05*

* Non Significant P > 0.05

Table (7)

The effects of Dapsone Therapy on serum creatinine and Blood urea in rheumatoid arthritis patients expressed as range, mean and S.D.

		Serum Creatinine umol / L .	Blood urea mmol / L
Before Dapsone No. 20	Range	102 to 65	6.2 to 3.8
	Mean	84.50	4.69
	SD	10.61	0.70
After Dapsone No. 20	Range	100 to 66	6 to 4
	Mean	86.05	4.75
	SD	9.21	0.54
P		> 0.05*	> 0.05*

* Non Significant P > 0.05

Table (8)

The effects of placebo Therapy on certain clinical parameters expressed range, mean, and SD before and after Therapy

		Morning stiffness (min)	Number of painful joints	Number of Swollen joints	Ritchie articular index	Grip strength (mm Hg)	PIP.J Circumferenc (mm. total of 10 joints)
Before placebo No 20	Range	120 to 45	16 to 8	9 to 4	40 to 28	85 to 33	598 to 554
	Mean	69.75	10.75	6.45	31.35	60	582.4
	SD	26.33	2.14	1.60	3.52	15.81	11.90
After placebo	Range	120 to 30	13 to 8	8 to 3	36 to 28	80 to 40	600 to 565
	Mean	64.25	10.25	5.45	30.35	60	581.55
	SD	23.96	1.33	1.53	2.47	12.97	9.41
P		> 0.05	> 0.05	> 0.05	> 0.05	0	> 0.05

Table (9)

The effects of placebo therapy on Haemoglobin, total and differential white cell count in rheumatoid arthritis patients expressed as range, mean, and S.D.

		Haemoglobin % gm / 100 ml	Total White cell Count	Differential white Cell Count.				
				Neutrophil %	Lymphocyte %	Easinophil %	Basophil %	Monocyte %
Before placebo No 20	Range	13 to 10	8 to 4.9	70 to 52	43 to 25	3 to 1	1 to 0	4 to 1
	Mean	11.01	6.230	59.95	36.05	1.95	0.1	2.45
	SD	0.80	1.082	5.18	5.26	0.68	0.30	0.82
After placebo No 20	Range	12.8 to 10	8.5 to 5	70 to 54	42 to 26	3 to 1	1 to 0	5 to 1
	Mean	11.06	6.250	59.65	35.5	2.1	0.3	2.45
	SD	0.77	0.907	4.31	3.94	0.64	0.47	0.94
P		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	0

Table (10)

The effects of placebo Therapy on E.S.R & C.R.P. and Rheumatoid factor (latex Titre) in R.A. patients expressed as range, mean and SD.

		ESR mm/hr (westergren)	CRP mg/dL	RF (latex titre) IU/ml
Before Placebo No. 20	Range	80 to 38	7 to 3.2	160 to 0
	Mean	50.2	4.85	100
	SD	8.50	1.08	54.28
After Placebo No. 20	Range	85 to 40	6.6 to 3.5	160 to 0
	Mean	48.65	4.84	105
	SD	6.53	0.85	52.26
P		> 0.05	> 0.05	> 0.05

Table (11)

The effects of placebo therapy on alanine aminotransferase (ALT). Aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in RA patients expressed as range, mean and SD.

		ALT U / L	AST U / L	ALP U / L
Before placebo No. 20	Range	14.2 to 6	12.3 to 5.9	95 to 32
	Mean	9.3	9.05	56.3
	SD	2.07	1.87	11.35
After placebo No. 20	Range	15.3 to 6.8	13 to 7.2	105 to 30
	Mean	9.45	9.55	56.35
	SD	1.57	1.39	9.04
P		> 0.05	> 0.05	> 0.05

Table (12)

The effects of placebo therapy on serum creatinine and blood urea in R.A. patients expressed as range, Mean and SD.

		Serum Creatinine ummol / L	Blood Urea mmol / L
Before Placebo No. 20	Range	100 to 57	6.4 to 3.5
	Mean	83.75	4.7
	SD	8.71	0.42
After Placebo No. 20	Range	98 to 60.5	6.6 to 3.2
	Mean	83	4.67
	SD	5.71	0.38
P		> 0.05	> 0.05

Table (13)

Comparison between The effects of Dapsone and placebo Therapy on certain clinical parameters in RA. patients expressed as mean and S. D.

		Morning Stiffness (min)		Number of painful joints		Number of Swollen joints		Ritchie articular index		Grip strength (mm Hg)		PIP Circumference (mm.)	
		B	A	B	A	B	A	B	A	B	A	B	A
Dapsone N 20	Mean	68.25	28.5	11.5	4.5	6.75	2.3	32.95	13.65	59	64.25	579.8	563.8
	SD	25.97	8.75	1.88	1.24	1.62	1.13	3.98	3.07	13.33	11.50	11.21	12.68
Placebo N 20	Mean	69.75	64.25	10.75	10.25	6.45	5.45	31.35	30.35	60	60	582.4	581.55
	SD	26.33	23.96	2.14	1.33	1.60	1.53	3.52	2.47	15.81	12.97	11.90	9.41
P		>0.05	<0.001	>0.05	<0.001	>0.05	<0.001	>0.05	<0.001	>0.05	>0.05	>0.05	<0.001

Table (14)

Comparison between the effects of Dapsone and placebo therapy on Haemoglobin, and Total and differential white cell count in R.A. patients expressed as mean and S.D.

		Haemoglobin % gm / 100 ml		Total white cell count		Differential white cell count									
						Neutrophil %		Lymphocyte %		Eosinophil %		Basophil %		Monocyte %	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A
Dapsone	Mean	11.14	10.29	6790	6965	60.7	60.3	34.3	34.6	2.4	2.4	0.05	0.15	3.05	3.15
N 20	SD	0.86	0.69	1.466	1467	7.39	6.59	6.24	5.95	0.88	0.94	0.22	0.37	1.099	1.089
Placebo	Mean	11.01	11.06	6230	6250	59.95	59.65	36.05	35.5	1.95	2.1	0.1	0.3	2.45	2.45
N 20	SD	0.80	0.77	1082	0907	5.18	4.31	5.26	3.94	0.68	0.64	0.30	0.47	0.82	0.94
P		> 0.05	< 0.001	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Table (15)

Comparison between the effects of Dapsone and placebo Therapy on E.SR & C.RP and rheumatoid factor (Latex titre) in rheumatoid arthritis patients expressed as mean and SD.

		ESR mm / h r		CRP mg / dl		RF (latex titre) IU / ml	
		B	A	B	A	B	A
Dapsone	Mean	49.25	26.7	5.11	2.98	104	100
No. 20	SD	6.40	5.64	1.01	0.64	57.16	49.42
Placebo	Mean	50.2	48.65	4.85	4.84	100	105
No. 20	SD	8.50	6.53	1.08	0.85	54.28	52.26
P		>0.05	<0.001	>0.05	<0.001	>0.05	>0.05

Table (16)

Comparison between the effects of Dapsone and placebo Therapy on alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in RA patients expressed as mean and SD.

		ALT U / L		AST U / L		ALP U / L	
		B	A	B	A	B	A
Dapsone	Mean	9.15	9.35	10.05	10.35	55.9	56.8
No. 20	SD	2.53	1.92	1.87	1.81	13.49	12.56
Placebo	Mean	9.30	9.45	9.05	9.55	56.30	56.35
No. 20	SD	2.07	1.57	1.87	1.39	11.35	9.04
P		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Table (17)

Comparison between The effects of Dapsone and placebo Therapy on serum creatinine and blood urea in rheumatoid arthritis patients expressed, Mean and SD .

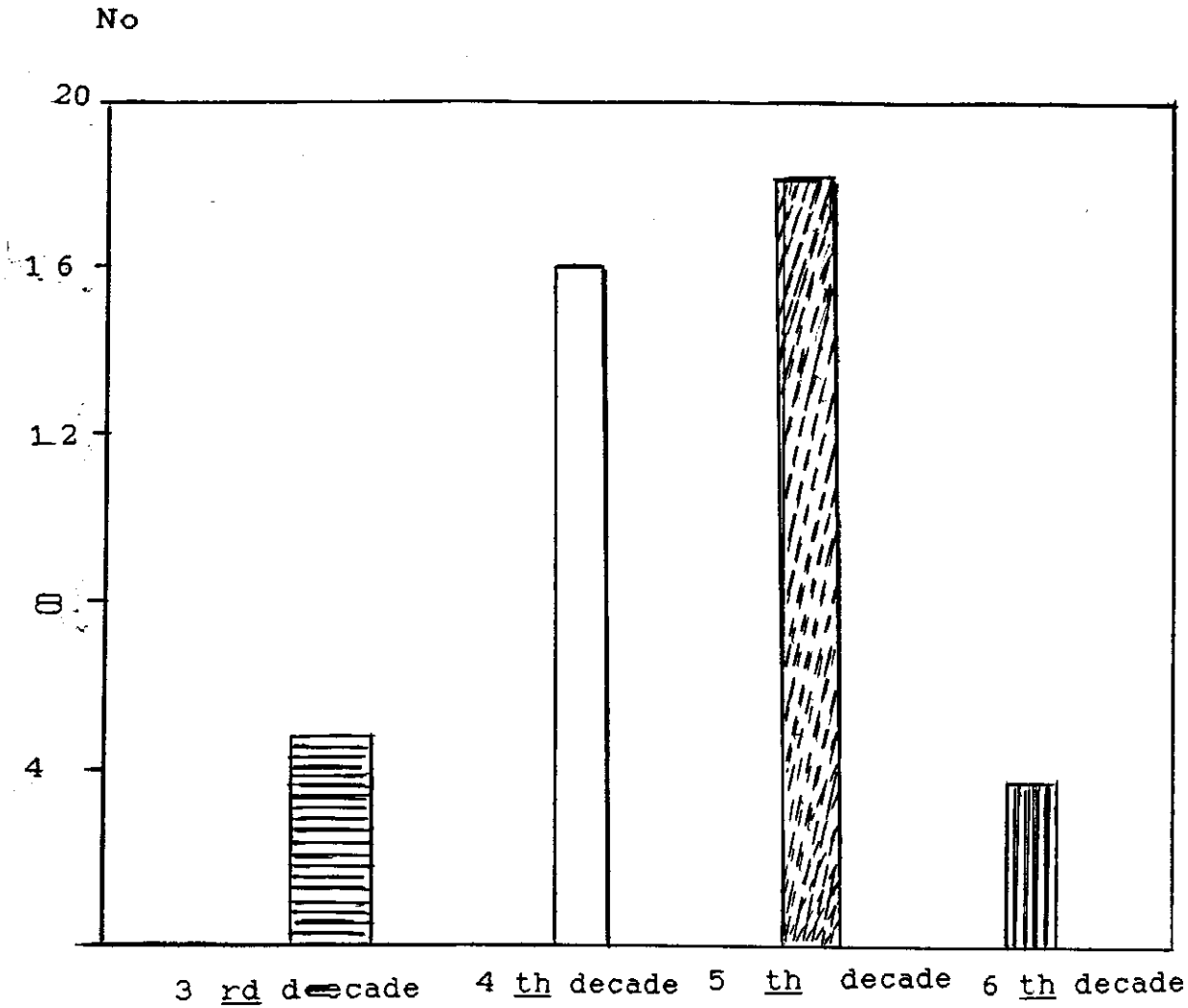
		Serum Creatinine ummol / L		Blood urea m mol / L	
		B	A	B	A
Dapsone	Mean	84.5	86.05	4.69	4.75
No. 20	SD	10.61	9.21	0.70	0.54
placebo	Mean	83.75	83	4.70	4.67
No. 20	SD	8.71	5.71	0.42	0.38
P		>0.05	>0.05	>0.05	>0.05

Table (18)

Shows The Side effects commonly encountered during This study .

Side effect	Week (4)		Week (24)	
	Dapsone	Placebo	Dapsone	placebo
Rash, pruritis	2	4	0	3
Gastrointestinal upset Neusea, dyspepsia	6	6	1	4
Dysnea, palpitation	7	4	1	2
Headache, dizzness	7	6	0	2

Fig (1) Distribution of rheumatoid cases according to sex .



Fig(2) Incidence of Rheumatoid Arthritis According to age

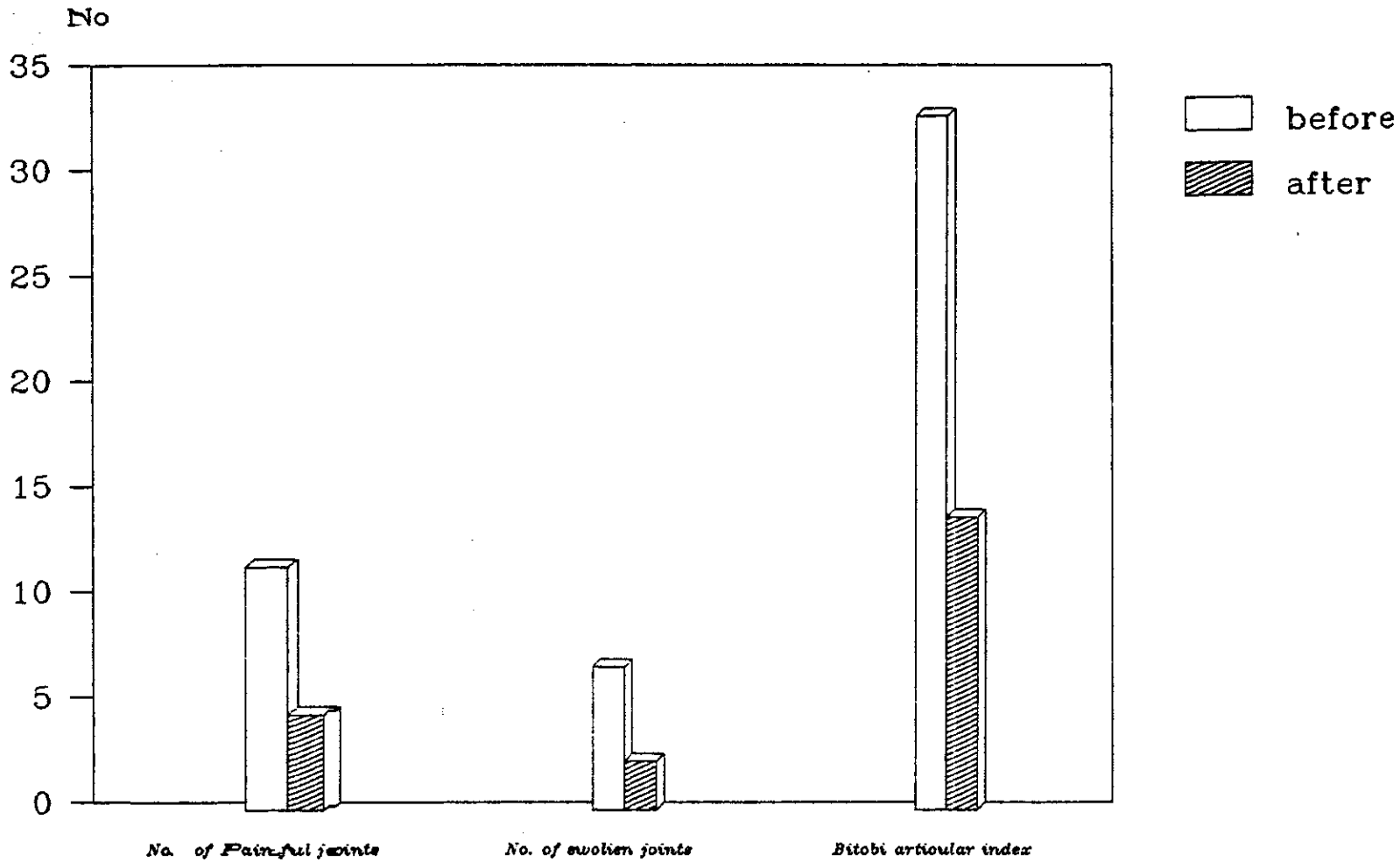


Fig (3) Effect of Dapsone Therapy on certain joint parameters

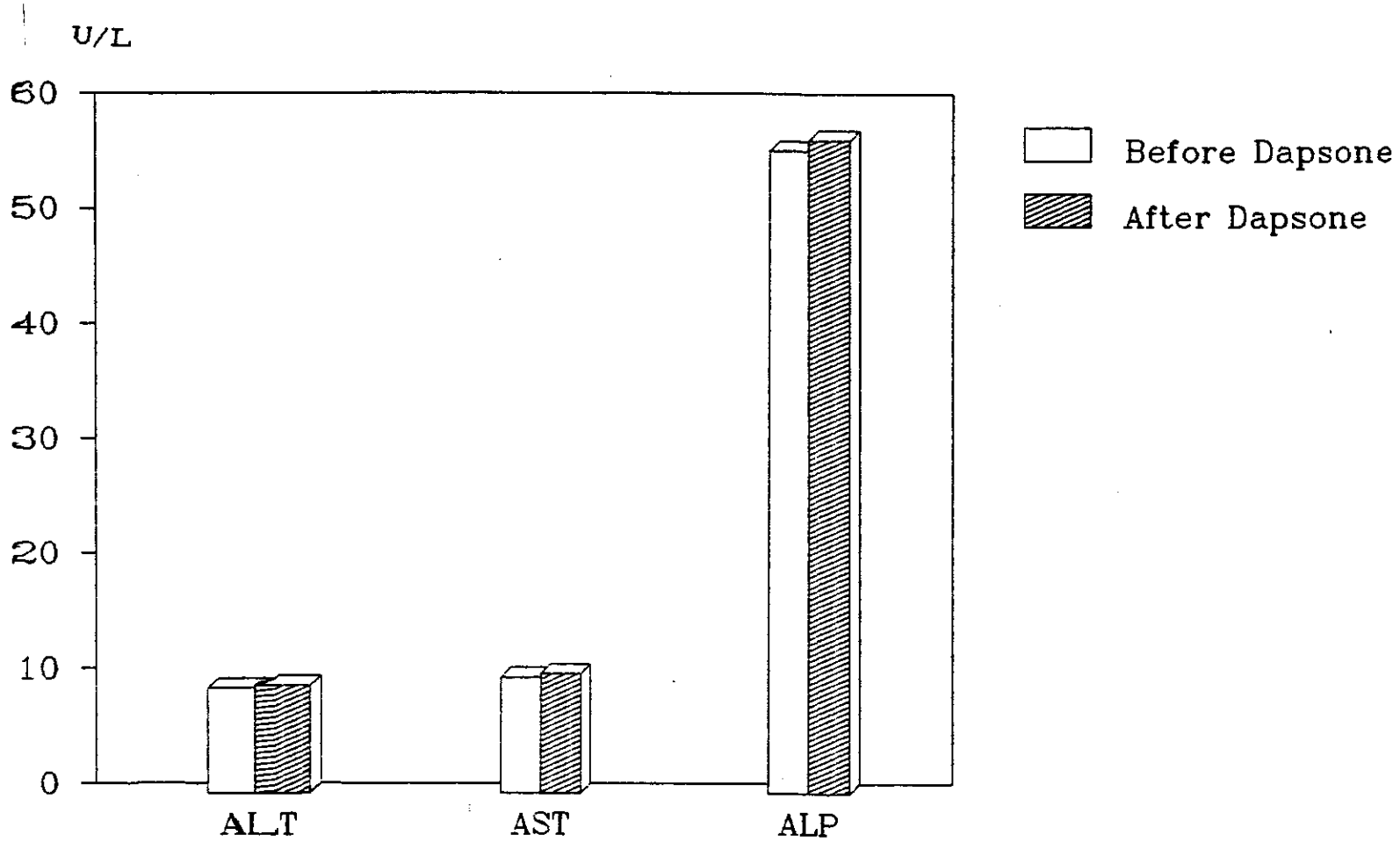


Fig (4) The effect of Dapsone on ALT, AST, and (ALP)

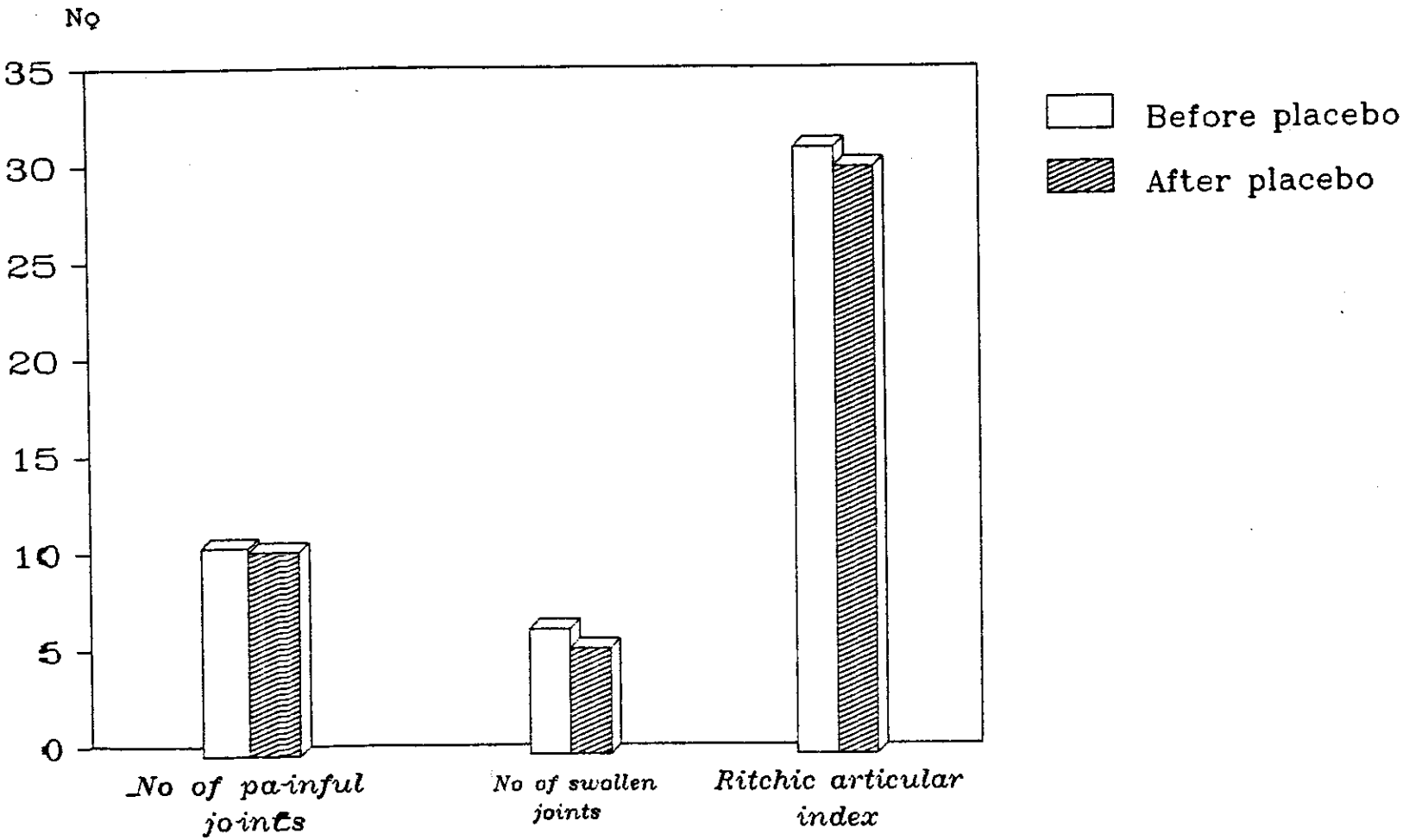


Fig (5) The effect of placebo therapy on Certain joint paramrters

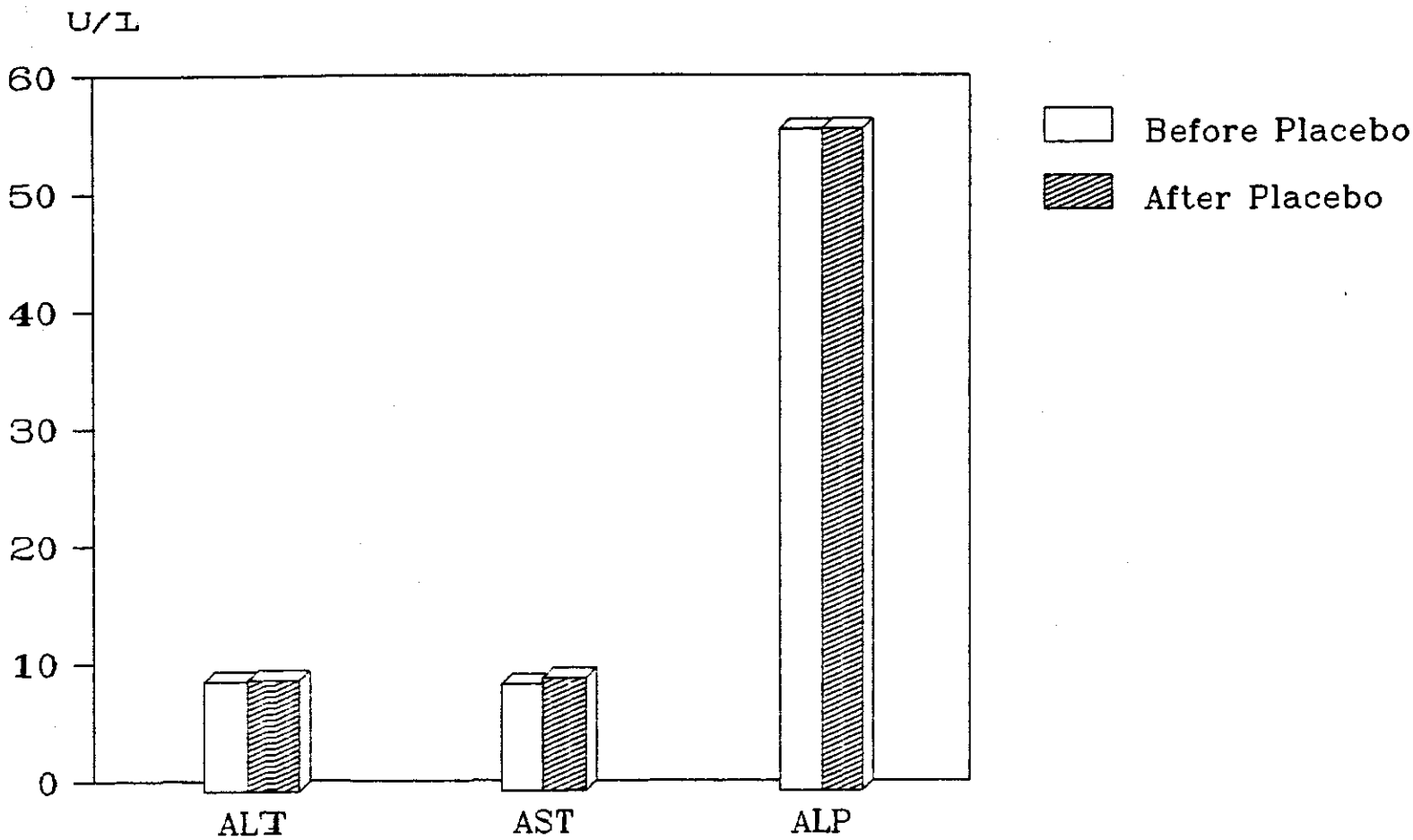


Fig (6) The effect of placebo on ALT, AST and ALP

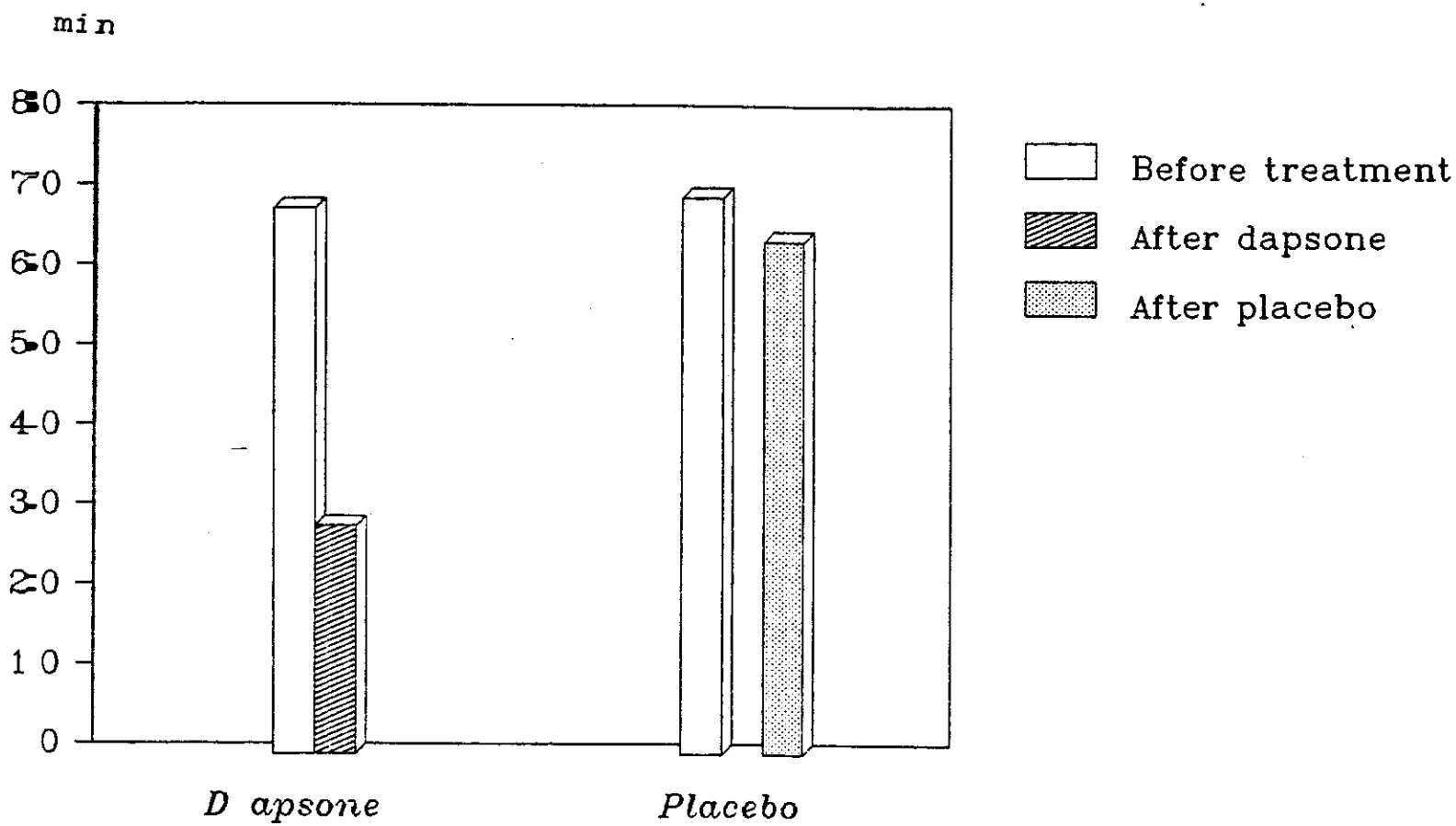


Fig (7) The effect of dapsone and placebo on the duration of morning **STIFFNESS** *in R.A.*

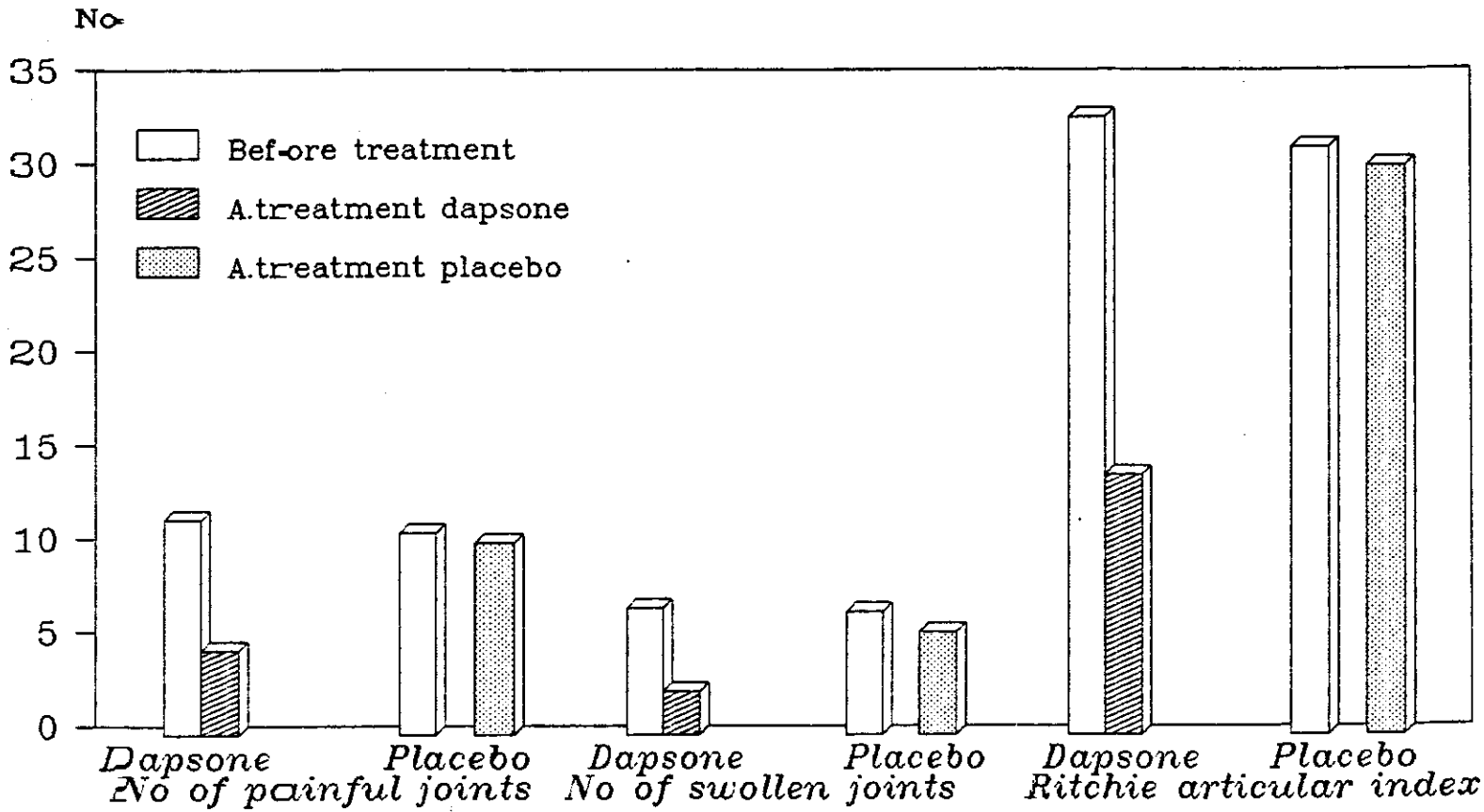


Fig (8) The effects of dapsone and placebo therapy on certain joint parameters of rheumatoid arthritis

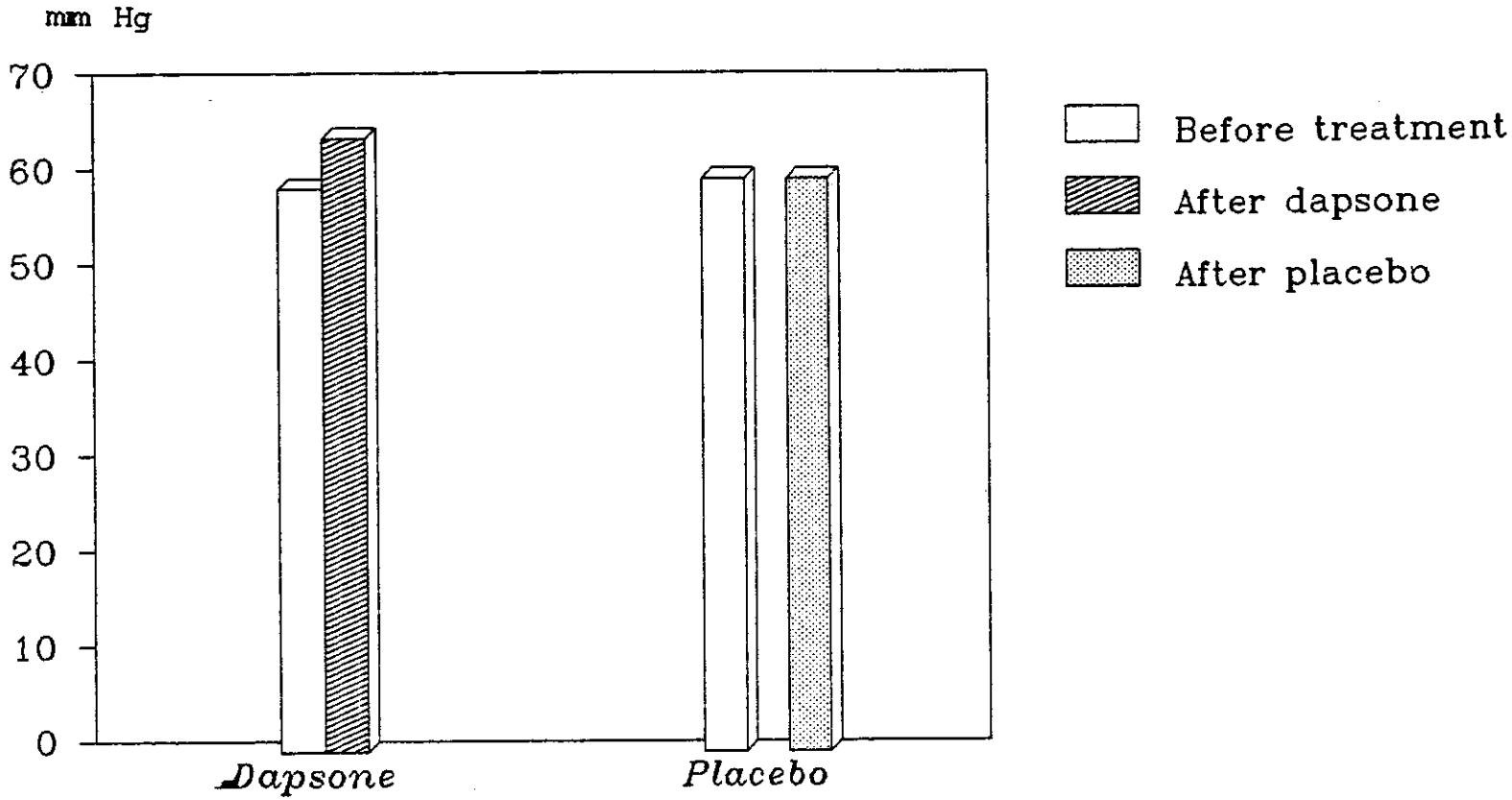


Fig (9) The effect of dapsone and placebo therapy on grip strength in R.A. patients

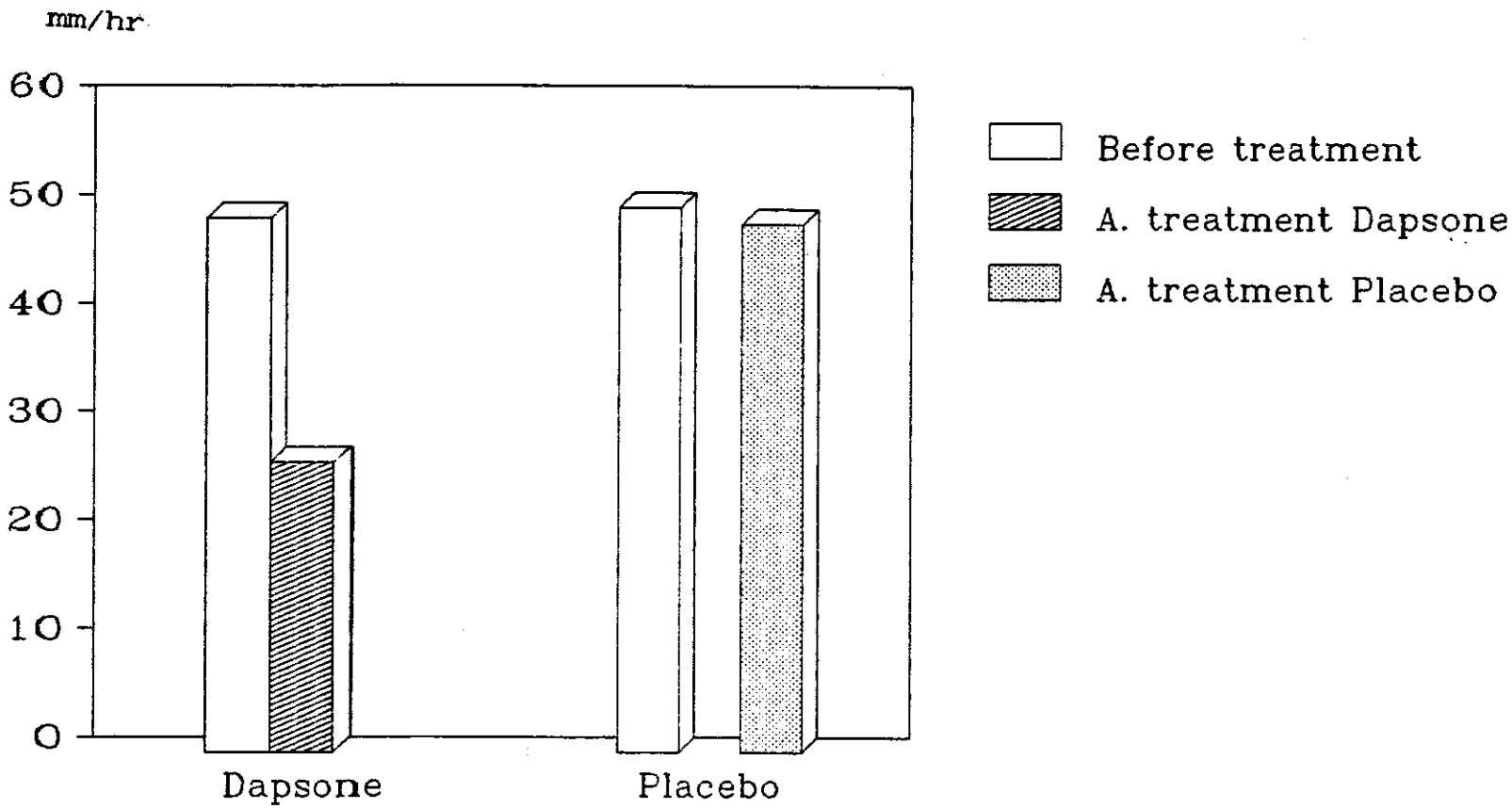


Fig (10) The effect of Dapsone and Placeb_o on ESR. in rheumatoid arthritis patient

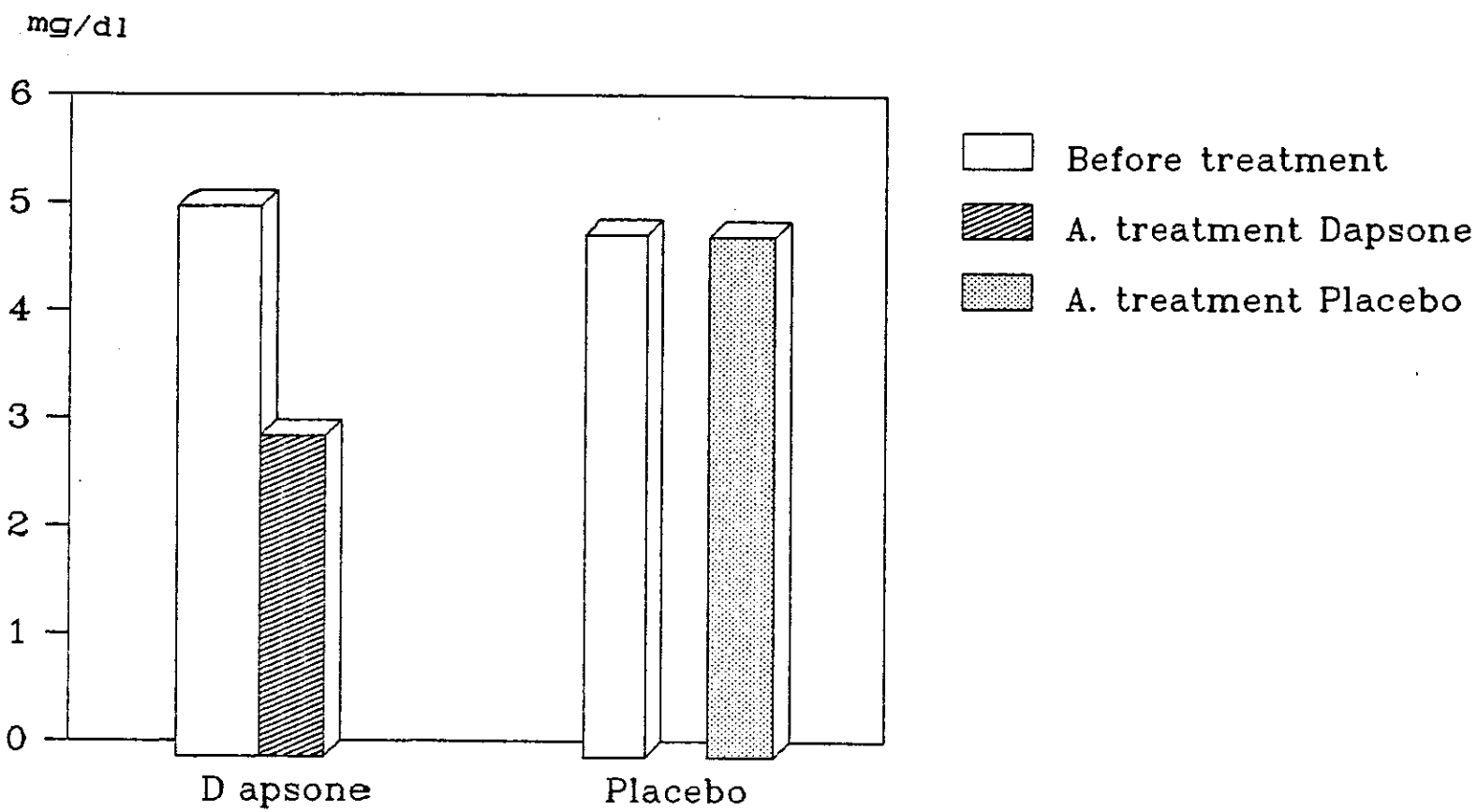


Fig (11) The effect of Dapsone and Placebo on C-R-P in rheumatoid arthritis patient

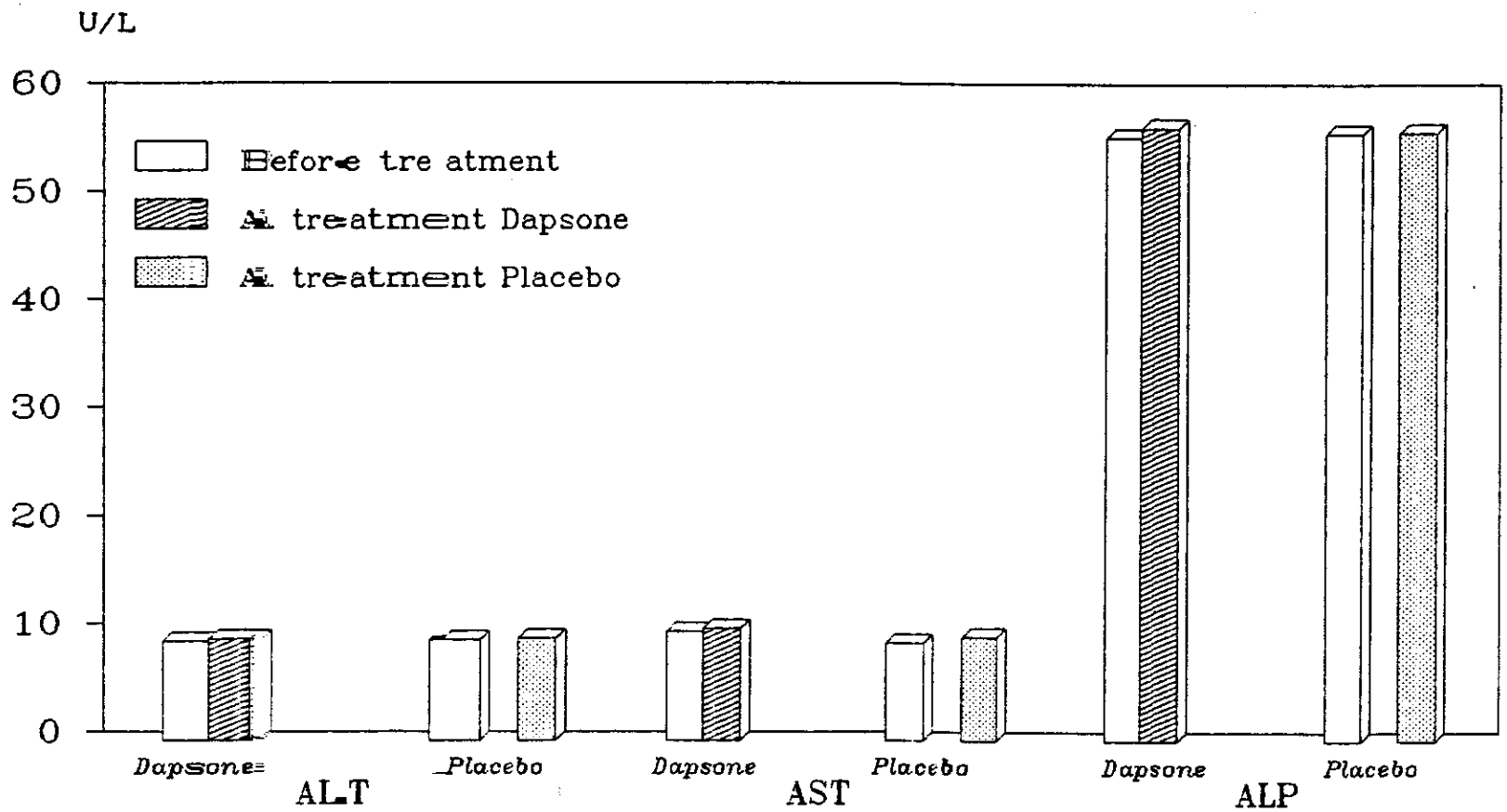


Fig (12) The effect of Dapsone and Placebo Therapy on ALT, AST and ALP in rheumatoid arthritis patients

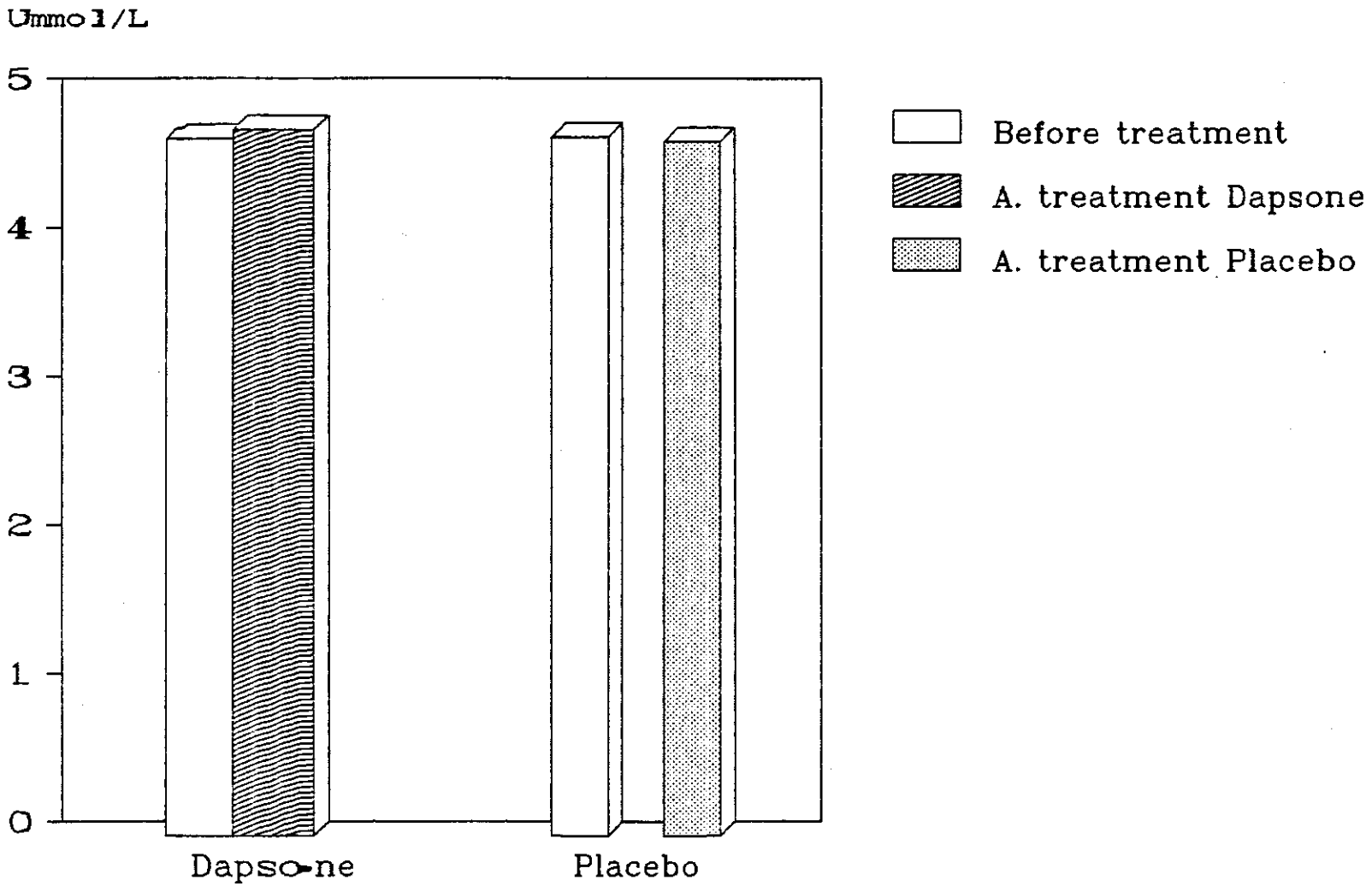


Fig (13) The effect of Dapsone and Placebo on SERUM CREATININE in rheumatoid arthritis patient

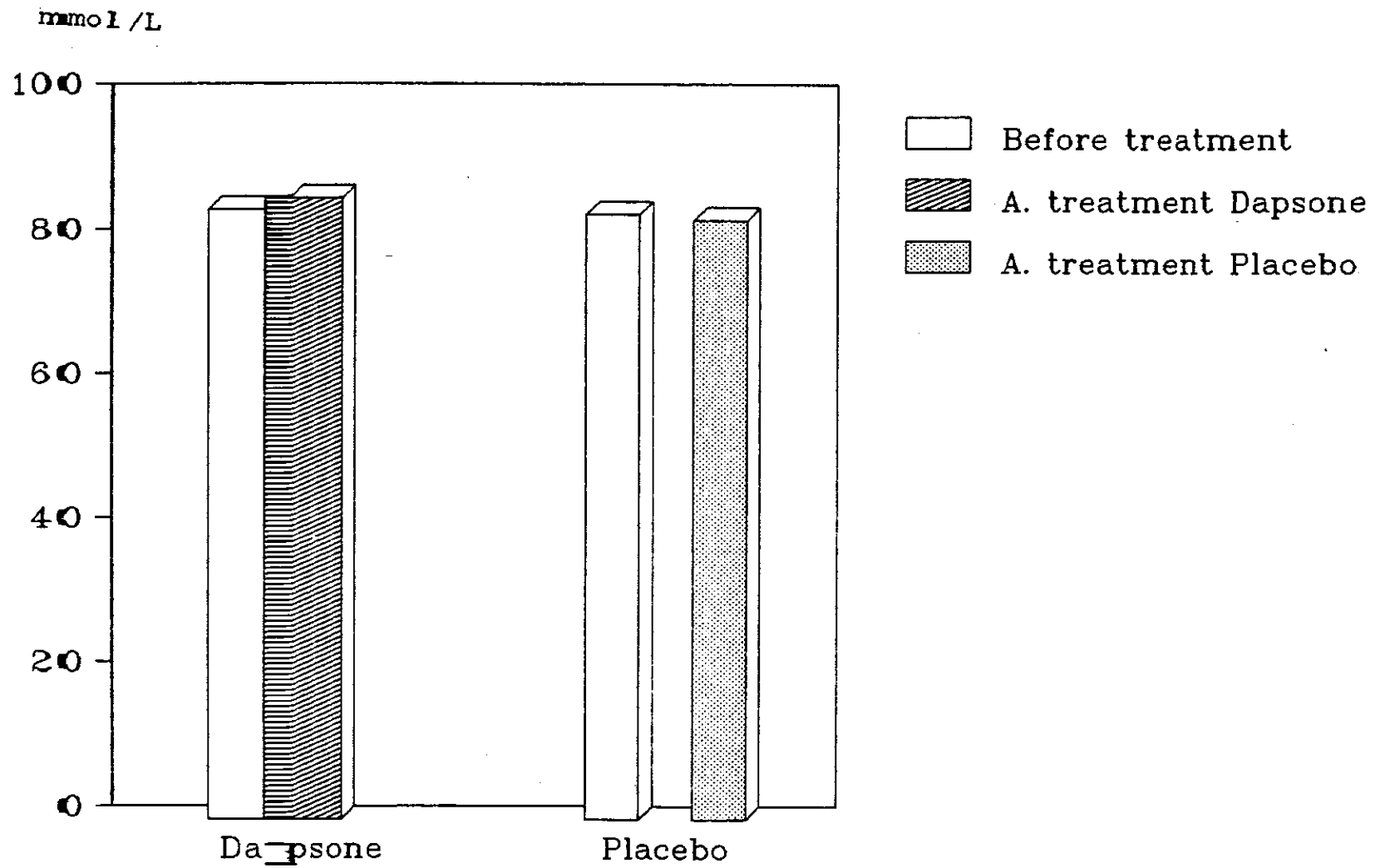


Fig (14) The effect of Dapsone and Placebo on BLOOD UREA in rheumatoid arthritis patient

DISCUSSION

Rheumatoid arthritis is a common disease with widely varying severity. A significant proportion of patients have a chronic course with progressive joint destruction and disability (McKenna. 1988).

Proper management of rheumatoid arthritis results in the maintenance or restoration of the patient to a state of useful and harmonious function with her enviroment (Ruddy, 1985).

Drug therapy forms only part of the overall management of a patient with rheumatoid arthritis, it may be the most effective, it may also be the most distastrous (Holt, 1986).

Although the choice of treatment for rheumatoid arthritis has increased little, there is a continuing trend towards more active management. Many rheumatoid patients with early disease are now being given slow-acting remission-inducing drugs in an attempt to slow disease progress, but evidence of long term benefit is lacking (Halberg, 1984 and Scott et al., 1987).

With rheumatoid arthritis treatment, usually there are two common mistakes, either the patients are kept on aspirin like drugs for long peroid in the face of obvious and severe

deterioration, or corticosteroids are given early with considerable immediate effect but at greater cost later on (Constable et al., 1973).

In the present study cases of active rheumatoid arthritis were selected using the criteria of American Rheumatism Association (1958) & its modification by Ropes (1959).

The sex incidence of rheumatoid arthritis in the present study was 6 females to 1 male. This is different from the observations of Duthie et al. (1955) and Felming et al. (1976) in which the ratio tends to vary from 2:1 to 4:1, it was even believed that rheumatoid arthritis occurs with equal incidence in both sexes.

The cause of female predominance is unknown, although women are more reactive in most immunologic parameters (Rhodes et al., 1969). The relatively high female ratio in the present work could be due to small number of studied cases.

In the present work the mean age at onset was 41.09 $\pm$7.16 years old with a peak incidence in the 4th and 5th decades of age. In the study of Felming et al. (1976) the

age of onset follows a normal distribution curve with its peak in the 5th decade, but no age is exempt.

Although the relation of age at onset to the severity of rheumatoid arthritis gave no significant conclusions. Felming et al. (1976) stated that the older age of onset, the poor prognosis, but other studies Showed no difference in clinical progression of the disease in relation to age of onset (Feigenbaum et al., 1979 and Leuukkainen et al., 1983).

The distribution of the affected joints in this study were 93% hand joints 88% wrist joints and this was the more frequent involved joints. While the less frequent involved joints were the cervical, temperomandibular and hip joints their frequency of involvement were 9%, 12% and 12% respectively. This is in agreement of the report of Emonds and Hughes (1985) who described the frequency of joint involvement in rheumatoid arthritis as 90% hand joints and 85% wrist joints. While the less frequent involved joints were temperomandibular, Neck and hip joints. Also Moll (1987) described the pattern of arthritis in rheumatoid patients with predominant involvement of the hand joints and wrist joints. While the elbow, cervical spine and hip joints were less affected, and temperomandibular joint was involved at some stages of the disease.

The dominence of hand and wrist joints involvement support the view that, the degree of joint involvement is a function of the forces acting on that joint, (Dickson et al., 1973) the special prediliction for the hand joints involvement were previously suggested to be related to trauma (Glick, 1967 and Bland and Eddy, 1968).

Assessment of disease activity is a difficult task, especially that the main disease features as the pain and joint stiffness are hard to measure and subject to large inter and intra-observer error.

The main use of assessment of disease activity lies in monitoring anti-rheumatic drugs and other therapeutic procedures, whether for individual patients or group therapy.

Assessment of any therapy in rheumatoid is drastically complicated by spontaneous remissions, and exacerbations in disease activity. So accurate sequential assessment of patients is important (Dick and Goodacre, 1985).

Therefore, assessment of rheumatoid disease activity can be broadly divided into short term (1-6 months), medium term (6-24 months), and long term assessment (24 months on wards), (Kirwan et al., 1983). Short term assessment ismainly measuring pain, stiffness (duration of morning stiffness in minutes, articular index (Ritchie, 1968), grip strength, and

joint swelling (proximal interphalangeal joint circumference), as well as laboratory measurement of erythrocyte sedimentation rate, haemoglobin concentration and rheumatoid factor titre. Medium term attention is directed to change in the disease process. Where radiology plays a very important role with the promise of developing technology, radiology may be considered the most practical method despite the unclear relationship between the erosive changes and the other features of rheumatoid disease (Huskisson et al., 1983) radiology is possibly augmented by measures of acute phase proteins. Long term outcome in rheumatoid disease is viewed as a five dimensional structure of death, disability, discomfort, drug side effects, and economic effects.

In our blind study, to evaluate the efficacy of dapsone in relation to placebo in treating rheumatoid arthritis patients we used some parameters for short term studies (24 weeks duration).

Dapsone in the present study was given in a dose of 50 mg per day for a week followed by 100 mg daily thereafter and placebo was administered as tablets identical to dapsone tablets.

There was an insignificant correlation ($P > 0.05$)

between the duration of morning stiffness and the other clinical parameters. These results was in agreement with Rhind et al. (1980) who found insignificant. Correlation between morning stiffness and articular index and grip strength.

We found that, dapsone produced a highly significant reduction ($P < 0.001$) in the duration of morning stiffness when compared to placebo therapy. This is in accordance to the findings of Swinson et al. (1981) who found a significant improvement in morning stiffness in patients receiving dapsone when compared to placebo, also Fowler et al. (1984) found a significant improvement in morning stiffness in both treatment groups (chloroquine and dapsone).

In this study, we found that, the number of painful joints, the number of swollen joints and the value of Ritchie articular index in the dapsone group were significantly decreased ($P < 0.001$) when compared to placebo group. This is in agreement with Swinson et al. (1981) who found that dapsone is effective in reducing joint tenderness as measured by a modified Ritchie articular index, also Fowler et al. (1984) found a significant decrease in the number of painful joints and a significant decrease in the value of Ritchie articular index.

We observed that there was a significant correlation (P < 0.05) between articular index and the other clinical and laboratory parameters. Moreover Dixon et al. (1988) showed that articular index is the best clinical measure for monitoring patients during short-term second line therapy in rheumatoid arthritis, and Rhind et al. (1980) found well correlation between articular index, and other clinical and laboratory parameters in rheumatoid arthritis patients, and are therefore judged to be the best clinical indices of changes in treatment with second line therapy.

In this study the grip strength was significantly correlated (P < 0.05) with articular index but not with the other clinical parameters.

Although Anderson et al. (1989) found that grip strength perform best in rheumatoid arthritis clinical trials, but Dixon et al. (1988) showed that grip strength measurement fared badly and can not be recommended in rheumatoid arthritis patients treated with second line therapy, and its continued use in clinical trials rests largely on its simplicity and rapidity (Deodhar et al., 1973).

On dapsone therapy, grip strength showed an insignificant increase (P > 0.05) when compared to placebo, this is in agreement with the findings of Swinson et al.

(1981) and Fowler et al. (1984) who found insignificant improvement in grip strength following dapsone therapy.

This parameter responds more slowly than most of the others as disease activity wanes, and therefore may not seem to be as useful in short term trials (McCarty, 1979) joint circumference, reflecting a single group of joints correlates poorly with the clinical and laboratory parameters, (Rhind et al., 1980) and Dixon et al. (1988) showed that joint size fared badly and can not recommend in rheumatoid arthritis patients treated with second line therapy. Moreover, Andreson et al. (1989) advised to eliminate proximal interphalangeal joint circumference from rheumatoid arthritis clinical trials.

In this study there was insignificant correlation ($P > 0.05$) between circumference of P.I.P. joints and other clinical and laboratory measurements.

The size of P.I.P. joints was followed beforeand after giving the specific line of therapy. On dapsone therapy the size of P.I.P. joints was significantly decreased ($P < 0.001$), when compared to the placebo therapy. This is in agreement with McConkey et al. (1976); Swinson et al. (1981); andFowler et al. (1984), who found that the size of P.I.P.Js was significantly decreased following dapsone therapy.

Laboratory measurements for assessment of disease before and after different treatment was stressed upon in this study.

Cart wright and Lee (1971) reported that in a chronic disease such as rheumatoid arthritis the anaemia could result from combination of many factors as failure of the reticulo-endothelial system to release iron or diminshed erythropoisis. Moreover Granan et al. (1973) stated that haemoglobin concentration tends to change in proportion to disease severity. While McCarty (1979) stated that the value of anaemia as a measure of rheumatoid activity is lessened by its presence in less than half the cases with active disease.

Haemoglobin concentration was studied before and after treatment. There was no evident relation between disease activity and the magnitude of haemoglobin concentration. Moreover there was insignificant correlation ($P > 0.05$) between haemoglobin concentration and ESR. Though McCarty (1979) found well correlation between haemoglobin concentration and erythrocyte sedimentation rate but no correlation with the duration of the disease.

There was a highly significant decrease ($P < 0.001$) in haemoglobin concentration following dapsone therapy when compared to placebo therapy Kelly and Griffith (1981) have confirmed the efficacy of dapsone but found much greater

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falls in haemoglobin and Swinson et al. (1981) found that the mean haemoglobin concentration fell by one gm/dl in the dapsone group over the 14 weeks of the trial. However, Grindulis and McConkey (1984) found that in the dapsone group the haemoglobin level fell by one gram in the first 6 weeks but thereafter tended to rise, probably as disease activity lessened, so they concluded that significant anaemia is probably not a common serious side effect providing that patients start with a reasonable haemoglobin level. So Fowler et al. (1984), McConkey et al. (1979) and Swinson et al. (1981) agreed that the haemolytic effect of dapsone were nevere severe enought to withdrawal of the drug and the level of haemoglobin thereafter, tended to rise. Moreover, DeGown (1967) stated that dapsone in a dose of 100 mg or less in normal healthy persons, and 50 mg or less in healthy individuals with glucose-6-phosphate dehydrogenase deficiency do not cause haemolysis.

The white cell count has been used in some schemes of evaluation, but its relation to disease activity, if any, has not been well studied, severely ill patients may have leukocytosis, leukopenia or a normal count (McCarty, 1979).

It was noticed that there was no association between the magnitude of leukocytosis and the degree of rheumatoid

activity. There was no evident relation between the elevated white cell count and the rise of sedimentation rate. These findings were contradictory to the statement of Farr et al. (1983) that leukocytosis could be used as a useful parameter in assessment of the degree of rheumatoid activity.

In the present study, dapsone produced insignificantly increase ($P > 0.05$) in the total white cell count when compared to placebo. Also changes induced by dapsone on the differential white cell count was insignificant ($P > 0.05$). This is in accordance to the findings of Fowler et al. (1984) and Swinson et al. (1981) who found no significant changes in mean values of white cell counts.

Dixon et al. (1988) showed that erythrocyte sedimentation rate was the best laboratory measure in rheumatoid arthritis patients treated by second line therapy. Also Anderson et al. (1989) found that E.S.R. is one of the parameters which perform best in rheumatoid arthritis clinical trials.

Erythrocyte sedimentation rate using westergren method was studied before and after treatment. There was evident relation between disease activity and the magnitude of E.S.R. There was a significant correlation ($P < 0.05$) between E.S.R. and articular index and grip strength. On the other hand

there was a significant correlation (P < 0.05) between E.S.R. and C-reactive protein. The present data at variance for the statement of Constable et al. (1975) that measurement of erythrocyte sedimentation rate is sometimes misleading. On the other hand these findings is in agreement with Haataja and Kalliomaki (1978) who found well correlation between E.S.R., C.R.P. and disease activity in R.A. and with other laboratory variables in this condition. In this study dapsone produced highly significant reduction (P < 0.001) in erythrocyte sedimentation rate when compared to placebo, this is in agreement with many trials of dapsone in rheumatoid arthritis (McConkey et al., 1976, 1979; Swinson et al., 1981; Fowler et al., 1984 and Grindulis and McConkey, 1984) who found a significant reduction in E.S.R. following dapsone therapy.

The C-reactive protein was found to be a more sensitive test because gold, penicillamine and prednisone had a greater effect on the C.R.P. than the ESR (Walsh et al., 1979).

In rheumatoid arthritis, CRP is present in all patients with clinical evidence of the disease and usually parallels the ESR closely (Baum and Ziff, 1985).

There was a highly significant reduction (P < 0.001) in C-reactive protein in patients receiving dapsone when

compared to placebo. This is in agreement with (McConkey et. al., 1976, 1979; Fowler et al., 1984 and Grindulis and McConkey, 1984) who found a significant reduction in C.R.P. following dapsone therapy.

A reduction in rheumatoid factor titres was not demonstrated in McConkey et al. (1976) although in Swinson et al. (1981) trial there was nonsignificant reduction in rheumatoid factor titres over the 14 weeks in patients treated with dapsone. In our study there was an insignificant alteration(P > 0.05) in latex titre following dapsone therapy. When compared to placebo therapy.

There was no relation between the degree of activity and the magnitude of latex titre, and sero negative patients could be present even with aggressive characteristics. This confirms with the statement of Dieppe et al. (1985) who suggested that rheumatoid factor level in the sera of patients with rheumatoid arthritis fluctuate and are not areliable guide to disease activity.

Minor biochemical abnormalities of liver function are frequent in patients with rheumatoid arthritis (Webb et al., 1979) and Whaley et al. (1970) found biochemical evidence of liver disease only in 0.7% of 997 patients with rheumatoid arthritis. Moreover Sullivan et al. (1978) stated that if

clinical liver disease does develop in patients with rheumatoid arthritis, the most likely explanation is drug toxicity.

Panayi (1982) reported that minor rises in alkaline phosphatase occured in RA reflecting more severe disease but did not correlate well with clinical evidence of disease activity. Dixon et al. (1980) found that the enzyme gammaglutamyl transpeptidase was significantly increased together with serum bilirubin in rheumatoid patients reflecting abnormal reticulo-endothelial function in this disease. They found that these levels correlated well with severity of the disease but not with activity of the disease.

In this study measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), before treatment were (9.15 + 2.54) U/L (10.05 + 1.88) U/L and (55.9 + 13.49) IU/L respectively.

The level of alanine aminotransferase (ALT) is in agreement with the findings of Webb et al. (1975) who found that in rheumatoid arthritis serum bilirubin and ALT were within normal levels and not defferent from control, and also the level of ALT and AST is similar to the results obtained by Malmquist and Reichard (1962) who found that in R.A., the levels of ALT and AST were within normal values.

The level of alkaline phosphatase was within normal value. This is in agreement with Duthie (1970) who stated that in rheumatoid arthritis, alkaline phosphatase is within normal limit, and any alteration in alkaline phosphatase indicate liver dysfunction (Kendal et al., 1970 and Cockal et al., 1971).

In this study insignificant changes ($P > 0.05$) in ALT, AST and ALP following dapsone therapy. When compared to placebo group was observed. This is in agreement with Fowler et al. (1984) who found no significant change in alkaline phosphatase and also Swinson et al. (1981) who found no significant alteration in liver function test after dapsone therapy.

Rheumatoid arthritis is not infrequently complicated by a spectrum of renal disorders. Proteinurea and marked renal impairment should suggest the possibility of amyloidosis or analgesic nephropathy (Dick and Goodacre, 1985) clinically the most important problem is amyloidosis which is present in 5% of rheumatoid patients (Wegelius et al., 1979). The incidence of chronic interstitial nephritis and papillary necrosis are increased possibly as a result of consumption of various nephrotoxic agents in the treatment of R.A. Occasionally, arteritic changes may be seen (Heptinstall,

1983). Glomerulonephritis are usually associated with the use of gold and D-penicillamine (Helin et al., 1986). Honkanen et al. (1987) observed membranous glomerulonephritis in rheumatoid patients not related to drug therapy.

In this study the level of blood urea and serum creatinine were within normal level, and there was no significant changes ($P > 0.05$) after dapsone therapy. When compared to placebo these findings are contradictory to the statement of Nived et al. (1983) that serum creatinine concentration in rheumatoid arthritis, where measured in patients with normal or impaired renal function was lower than in matched controls, probably because of the smaller muscle mass of R.A. patients. While Honkanen et al. (1987) found that 25% of their rheumatoid patients showed higher serum creatinine levels and lower creatinine clearance. On the other hand Dixon et al. (1981) observed a nonsignificant difference in the levels of urea and creatinine between sero +ve and sero - ve rheumatoid arthritis.

Side effects of dapsone was minimal, dyspnea and palpitations seemed to be related to dapsone consumption. They occured early in the trial and may be caused by haemolysis. These effects were never severe enough to warrant withdrawal of the drug. Headache would seem to be

another dapsone-related side effect on of the most serious toxic effect is haemolysis due to an oxidant effect on red cell membranes, haemolysis is demonstrated by the falls in haemoglobin level and therefore a moderate or severe anaemia would seem to be a contraindication to use of dapsone. Agranulocytosis is a rare side effect of dapsone. It has seldom been reported. Though dapsone has been used for many years in leprosy and dermatitis herpitiformis. However, a number of instances occured among soliders having dapsone as a malaria prophylactic (Ognibene, 1970).

In this study no case of agranulocytosis was found.

The lack of unwanted effects reported by patients on dapsone at the end of the trial compared to the number reported by placebo patients is striking. This discrepancy may be related to the cessation or reduction of anti-inflammatory analgesic consumption.

Finally we try to equate the action of dapsone in rheumatoid arthritis, with its action in dermatitis hereptiformis, a skin disease clearly associated with an enteropathy and respending to both dapsone and gluten-free diet. The effect of dapsone in dermatitis herpetiformis is more immediate and there is no evidence to date that gluten sensitivity is related to the pathogenesis of rheumatoid

arthritis (Dyer et al., 1981 and Carty and Green, 1976).

The mode of action of dapsone may be due conjectural inhibition of lysosomal enzymes that has been demonstrated in animal experiments (Barranco, 1974). Although action of dapsone on red cell membranes would suggest that the inhibition is not brought about by stabilising lysosomal membranes, (Swinson et al., 1981). An immunosuppressant action has been suggested in leprosy, where a low dose is antimicrobial and a larger dose immunosuppressant and capable of modifying. The borderline leprosy reaction (Barnetson et al., 1976). Its antimicrobial action in leprosy is also associated with the conversion of rheumatoid factor-positive leprosy to seronegativity (Ellis, 1978). A reduction in rheumatoid factor titres was not demonstrated in McConkey et al. (1976, 1979) and in Fowler's et al. (1984) reports and also in our study there was an insignificant alterations in rheumatoid factor titres over the 24 weeks in patients treated with dapsone.

Our results go hand in hand with the reports of McConkey et al. (1976, 1976), Swinson et al. (1981), Fowler's et al. (1984) and Grindulis and McConkey (1984), that dapsone exerts a suppressive effect in rheumatoid arthritis. These reports comparing the effect of dapsone with gold, penicillamine,

chloroquine and sulphasalazine which may have amore profound effect on the disease, then amere relief of symptoms, suggested that dapsone may be a useful alternative treatment for rheumatoid arthritis.

We recommend that a more prolonged trial with a larger number of patients to report the efficacy of dapsone, as rheumatoid arthritis is a chronic disease and therapy must be given throughout the patient's life. Also management of rheumatoid arthritis needs a strategy to control that systemic disease with individual variation.

SUMMARY AND CONCLUSIONS

- The use of dapsone in the treatment of rheumatoid arthritis is still debatable. The aimed of this study is to evaluate the role of dapsone in the disease.

- 43 patients having rheumatoid arthritis were selected from the outpatient clinic Benha University Hospitals. They were 37 females and 6 males with age ranging from (32 to 60) years old (mean 46.13 $\pm$ 7.55 years). The selected cases fullfilled the criteria for diagnosis of rheumatoid arthritis according to the American Rheumatism Association (1958) and its modification by Ropes et.al, (1959)

- Gold, penicillamine or other suppressive agents were not administered for at least 3 months before the start of the trial patients on corticosteroids were admitted. The dose of corticosteroids or any orally administered anti-inflammatory analgesic drugs had to be constant during the last month before entry into the trial.

- All patients were subjected to:

* Full history taking with special attension to the duration of morning stiffness.

locomotor system, counting the number of painful joints, the number of swollen joints, determination of joint tenderness by using Ritchie articular index, measurement of grip strength of both hands using a modified sphygmomanometer, measurement circumference of the proximal interphalangeal joints (Total 10 joints in mm.).

* laboratory investigations including haemoglobin concentration, white cell count (Total and differential), erythrocyte sedimentation rate (westergren method), C-reactive protein using immunodiffusion method, Rheumatoid factor titre (latex titre), alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum creatinine and blood urea.

- Examination was done before starting treatment and a follow up was done monthly for 6 months duration.

- Patients were randomly allocated into two treatment groups:

22 patients received dapsone and 21 received placebo. The dapsone was administered in a dose of 50 mg a day for a week and 100 mg daily thereafter.

Any therapy, especially anti-inflammatory analgesics was noted during the trial and special instruction for patients

to maintain their pretrial dose of anti-inflammatory analgesics.

- Three patients were excluded from the trial. Two from dapsone group one because of side effect and the second owing to treatment inefficacy, and one from placebo group because of treatment inefficacy.

- At the end of trial. assessment was judged in every group according to both clinical and laboratory parameters.

- The results of clinical parameters of our R.A. patients were as follows:

* The duration of morning stiffness in the dapsone group showed a highly significant decrease (P < 0.001) when compared with the placebo group.

* The number of painful joints and swollen joints in the dapsone group showed a highly significant decrease (P < 0.001) when compared to the placebo group.

The value of Ritchie articular index for the group receiving dapsone showed a highly significant decreased (P < 0.001) when compared with the group receiving placebo.

* Dapsone produced a nonsignificant increase (P > 0.05) in the grip strength when compared to placebo therapy.

* Dapsone produced a significant reduction (P < 0.001)

in the circumference of proximal interphalangeal joints when compared to placebo therapy.

The results of laboratory investigation of our R.A. patients were as follows:

- The haemoglobin concentration in the dapsone group was highly significant decreased (P < 0.001) when compared to the placebo group.

- The white cell count showed an insignificant increase (P > 0.05) following dapsone therapy when compared to placebo therapy.

As regards differential white cell count, there was an insignificant changes (P > 0.05) following dapsone therapy when compared to placebo therapy.

ESR and CRP showed a highly significant decreased (P < 0.001) following dapsone therapy when compared to placebo therapy.

- There was insignificant change (P > 0.05) in latex titre following dapsone therapy when compared to placebo therapy.

- All changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were insignificant (P > 0.05) following dapsone therapy when compared to placebo therapy.

- The changes in serum creatinine and blood urea were insignificant (P > 0.05) following dapsone therapy when compared to placebo therapy.

We can conclude that dapsone produced a better improvement in controlling activity of rheumatoid arthritis with the delayed action.

- Inspite of the observed beneficial effects of dapsone in rheumatoid arthritis in this work yet aprolonged follow up period with a larger number of patients and further efforts are necessary in order to verify its real value in the treatment of rheumatoid arthritis.

Agnello, V., Tbanez de Kasip, G., arbetter, A.E., and spit, J.J.R. (1978):-
Significance of rheumatoid factors Cross reactive with DNA-protein (DNP). Arthritis & Rheum. 21.540.

Aitchenson, C.T., Peebles, C., Joplin, F., and Tan, E.M., (1980):-

characteristics of anti nuclear antibodies in Rheumatoid Arthritis. Arth.x Rheum., 23;528,

Amos, R.S., Crockson, R.A., and Crockson A.P., (1978):-
Rheumatoid Arthritis;C- reacdtive protein and erthrocyte sedimentation during initial treatment. Br. Med. J. 1:1386 .

Anderson, J.J., Felson, D.T., Meenan, R.F., and williams, H.J., (1989):-
which traditional Measures should be used in R.A. clinial trials? Arthritis and rheumatism vol.32 No.9 P.1093-1099.

Ansell, B.M., and loewl, G. (1977):-
Rheumatoid arthritis: general features. Clinics in Rheumatic Diseases. 3:385-401.

Ansell, B.M., (1978):-
Dermatomyositis and polymyositis in "Copeman's textbook of the rheumatic diseases" Ed. by scott. J.T., 5th edition. Living stone. London and New york. P.923.

Aptekar, R.G., Decker, J.L., Bujak, J.S., and wolff, S.M., (1973):-
Adult onest of Juvenile rheumatoid arthritis.Arthritis x Rheum. 16:715.

Arnett, F.C., Edworthy, S.M., and Block, D.A., (1988) The American Rheumatism Associtation-1987 revised criteria for The classification of rheumatoid arthritis. Arthritis x Rheum . :31:315-23.

Thermography in the assessment of inflammatory arthritis. Clin.Rheum .Dis.. 2:51

Bacon .P.A., (1982):-

Assessment in rheumatic diseases. In "Scientific Basis of Rheumatology "(Ed.) Panayi.G.s. Churchill, livingstone ,Edinburgh -London-Nework, P. 24

Barada F.A., O'Brien,W. and Horwitz,.A. (1981):-

"Scientific Basis of Rheumatology" edited by Panayi.G.S.. churchill,livingstone Edinburgh.London ,New York P. 70 Quoted by Panayi,G.S.

Barnes,C.G.and Mason,M.(1975):-

"Rheumatoid Arthritis " in : "An introduction to Clinical Rheumatology " Ed. by Mason .M. Currey .H.L.F.. 2nd edition.Pitnam medical. P:24

Barnes, C.G., (1986):-

Epidemiology of R.A., from Mason and Currey's Clinical Rheumatology edited by Currey, H.L.F.. 4 th ed, Churchill. Livingstone ,Edinburgh London and New York.4:43

Barnetson, R.S., Barnetson,C.,Pearson,J.M.H., and Rees,R.J.W.,(1976):-

Evidence for prevention of borderline leprosy reaction by dapsone ,Lancet: ii : 1171 - 2.

Barranco,V.P., (1974):-

Inhibitions of Lysosomal enzymes by dapsone . Arch Dermatol; 110:563-6

Bartholomew,L.E., and Bartholomew, F.N., (1979):-

Antigenic bacterial polysaccharide in rheumatoid synovial effusions. Arthritis & Rheum.22 : 969.

Baum,J.(1982):

Mediators of inflammation in:Panay. G.S.(ed) The scientific basis of rheumatology churchill.Livingstone, Edinburgh, P. 260-271.

Baum,J.,and Ziff,M., (1985):

"Arthritis and allied conditions" ed. by Mc Carty. D.J. Hollander.J.L.. 10th ed.. Lea. Febiger. philadelphia 40:643-659.

Beckett, Y.L., and Dinn, J.J., (1972):

Segmental demyelination in rheumatoid arthritis. Quarterly Journal of Medicine. New Series. 41:71.

Belin, D.C., Abeles, M., and weinstein, A., (1979):

Rheumatoid markers in The absence of arthritis. Journal of Rheumatology 6:293-299.

Bennett, J.C., (1981):

Aetiology of rheumatoid arthritis. in "Textbook of Rheumatology" ed by Kelly,W.N., Harris E.D., Ruddy, S. and Sledge, C.B., Saunders company vol. I P. 887.

Berger, L.S., and Ziter, F.M.H.(1972):

Calcifications withen enlarged subdeltoid bursae in rheumatoid arthritis: Case reports. Br.J.Radiol. 45:530.

Binder, H.J., O'Brien, W.M., Spiro, H.M., and Hollingsworth, J.W., (1966): Gluten and The small intestine in rheumatoid arthritis. Journal of The American Medical Association 195:857.

Blake, D.R., and Bacon, P.A., (1981):

Serum Ferritin and rheumatoid disease. Br.Med.J. 282:1273-1274.

Blake, D.R., Hall, N.D., Bacon, P.A., Dieppe, P.A., Halliwell B., and Gutteridge, J.M.C., (1981):

The importance of iron in rheumatoid disease. Lancet. 2:1142.

Bland, J.H., Van Buskirk, F.W.M., Tampas, J.P., Brown, E., and clayton, E., (1965):-

Astudy of roentgenologic criteria of R.A. of cervical spine.

The american J. of Roentgenology, Radium Therapy and Nuclear Medicine. 95:949.

Bland, J.H., and Eddy, W., M., (1968):-

Hemiplegia and rheumatoid arthritis.

Arthitis x Rheum.. 11:72.

Bland, J.H., (1974):-

Rheumatoid arthritis of The Cervical Spine. The journal of Rheumatology 2:319.

Boardman, P.L., and Hart, F.D., (1967):-

clinical measurement of The anti-inflammatory effects of Salicylates in rheumatoid arthritis.
B.Med.J.. 4:264-268.

Brewer, E.J. (1970):-

Juvenile Rheumatoid Arthritis.W.B. Saunders. philadelphia P.68.

Brod, J. and Sirota, J.H., (1948):-

J.clin Invest. 27:654, Quoted from practical clinical Biochemistry. vol. I, 5th ed. Varley.H. Gowenlock, A.H.. Bell, M., Eds. William Heinemann Medical Books. LTD. London. P.479. (1980).

Brown, M.M., Hadler, W.M., Sams, W.M., Wilson, J., and Snyderman, R., (1979):-

Rheumatoid nodulosis. Sporadic and familial diseases. Journal of Rheumatology. 6:286-292.

Buchanan, R.C.R., and Kraag, G. (1980):-

Is There a Lower incidence of deep Venous Thrombosis after Joint replacement in rheumatoid arthritis? Journal of Rheumatology 7:551-554.

Buchanan, W.W., and Tugwwll, P., (1985):-

Clinical evaluation in Rheumatic Diseases. from Arthritis and Allied Conditions ed. by McCarty. D.J. x Hollander, J.L., 10 th ed. Lea. febiger. philadelphia 7:156-175.

Buchanan, W.W., and Kean, W.F., (1986):-

"Articular and systemic manifestations of rheumatoid

Arthritis, "from Copeman's textbook of The Rheumatic Diseases. edited by Scott.J.T. 6th edition volume one. churchill. Livingstone. Edinburgh, London. Melbourne. and New York 26:653-705.

Buchnall, R.C., Davis.P., Bacon, P.A., and Verrier-Jones, J., (1982):-

Neutropenia in rheumatoid arthritis Studies on possible contributing factors. Annals of The Rheumatic Diseases. 41:242-247.

Bunch, T.W., O, Duffy, D, Tompkins, R.S., and O'fallon, W.M., (1984):-

Controlled Trial of hydroxychloroquine and D-penicillamine singly and in combination in The treatment of rheumatoid arthritis. Arthritis x Rheum. 27:267-276.

Bywaters, E.G.L., (1971):-

Still's disease in abult Ann Rheum. Dis. 30:121.

Carpenter, D.F., Golden A., and Roberts, W.V., (1967):-

Quadrivalvular rheumatoid heart disease associated with left bundle branch block. American Journal of Medicine 43:922.

Carson, A.A., (1985):-

Diagnostic tests:Rheumatoid Factor from "Textbook of Rheumatology" edited by Kelly, W .N. .Harris. E.D., Ruddy,s. and Sledge,C.B., 2nd edition. W.B. Saunders Company. philadelphia, London, Toronto, Mexicocity. Riodejaneiro, Sydney and Tokyo 44:664-697.

Cartwright, G.L., and Lee, G.R. (1971):-

The anaemia of chronic disorders. Br.J.Haematol., 21:147.

Carty, J.E., and Green, P.H.Y., (1976):-

Coeliac disease and auto-immunity. lancet: i:964.

Casagrande, P., (1965):-

Surgical rehabilitation of upper extremities. In "Progress in clinical rheumatology. edited by Dixon. A.st.J.. Little Brown and Co.Boston P.74.

Cassidy, J.t., Brody, G.L., and Martel, W., (1967):-

Monarticular juvenile rheumatoid arthritis. J.Pediat. 70:867.

Castenfors, H., Hulman, E., and Lovgren, O ,(1964):-

The bromosulphthalein-test(BSP) as ameasure of rheumatoid arthritis activity. Acta Rheumatol. Scand., 10:128-132.

Castillo, B. A., El Sallab, R. A., and Scott, J. T., (1965):-

physical activity. cystic erosions. and osteoporosis in rheumatoid arthritis.Ann.Rheum.Dis..29:522-527.

Chalmers. I. M. and Blair, G. S. (1973):-

Rheumatoid arthritis of The Temporomandibular joint. Aclinical and radiological study using circular tomography. Quartery journal of Medicine. New Series. 42:369.

Chamberlain, M. A., and Bruckner, F. E., (1970):-

Rheumatoid neuropathy. Annals of The Rheumatic Diseases. 29:609.

Chamberlain, M. A., (1986):-

Rehabilitation in The rheumatic diseases from "Compeman's textbook of the Rheumatic diseases" edited by Scott.J.T., 6th edition. volume two. churchill. livingstone. Edinburgh. London. Mellourne and New York. P. 1497 - 1516.

Champion, R. H., Reberts, S. O. B., and Pye, R. J., (1986):-

systemic Therapy from "textbook of Dermatology" 4th ed. vol.3. edited by Rook,A., Wilkinson. D.S., Edling,F.J.,F., and Champion,R.H., Black well scientific Publications. Oxford. London. Edinburgh.

Boston. PaloAlto, Melbourne. P. 2525.

Chaung, H.S., Ryan, L.M., Kozin, F., and McCarty, D.J., (1980):-

Synovial origins of rice bodies in joint Fluid.Arthritis x Rheum. 32:72-76.

Clemmensen, I., Holund, B., and Anderson, R., B., (1983):-

Fibrin and Fibronectin in rheumatoid synovial membrane and rheumatoid synovial Fluid., Arthritis and Rheumatism. 26:479-485.

Coblyn, J.S., Weinblatt, M., Holdsworth, D. and Glass, D. (1981):-

Gold-induced thrombocytopenia, a clinical and immunogenetic study of twenty three patients. Ann. Intern. Med. 95:178.

Cochrane, G.M., (1982):-

Rheumatoid arthritis: Vocational rehabilitation. Int. rehabil. Med. 4:148.

Cockel, R., Kendall, M.J., Becker, L.F., and Hawkins, C.F., (1971):-

Serum biochemical values in rheumatoid disease. Ann. Rheum. Dis., 30:166-170.

Collins, A., Ring, E., Cosh, J., and Bacon, P., (1974):-

Quantifcation of thermography in arthritis using multithermal analysis,I.The Thermographic index. Ann. Rheum. Dis., 33:113.

Colton, C., and Darby, A., (1970):-

Giant granulomatous lesions of The femoral head and neck in rheumatoid arthritis. Annals of rheumatic diseases 29:626.

Cone, III R.O., and Resnick, D., (1985):-

"Radiographic evaluation of articular disorders: "Textbook of Rheumatology" editied by Kelly, W.M., Harris,E.D., Ruddy, S., and sledge, C.B., 2nd ed.

Saunders Company. philadelphia. London. Toronto. Mexicocity. Riodejaneiro. Sydney and Tokyo. 39:569-608.

Constable, T.J., Crockson, R.A., Crockson, A.P., and McConkey, B.,(1975):-

Drug treatment of R.A., Lancet. 1:1176.

Convery, F.R., Conaty, J.P., and Nickel, V.L., (1971):-

Flexion deformities of The Knee in rheumatoid arthritis Clinical Orthopaedics. 74:90.

Corbett, M.,(1986):-

The management of rheumatoid disease from "Compeman's textbook of The Rheumatic Diseases" edited by Scott,J.T. 6th ed. volume one. churchill Livingst. -one. Edinburgh, London, Melbourne and New York. 27:706-719.

Crisp, A.J., Armstrong, E.D., Grahame, R., and Dussek, J.E., (1982):-

Rheumatoid lung disease, pneumothorax, and eosinophilia. Annals of The Rheumatic Diseases. 41:137-140.

Crissy, J.J., Gordy, E., Ferguson, J., and Lyman, R.B., (1970):-

A new technique for demonstration of skin Temperature patterns. J.Invest. Dermatol. 43:89.

Currey, H.L.F., Harris, J., and Mason, R.M., (1973):-

comparison of azathioprine, cyclophosphamide and gold in treatment of rheumatoid arthritis: Br.Med.J. 3:763-766.

Currey, H.L.F., (1975):-

Progressive systemic Sclerosis and polymyositis in "An introduction to clinical rheumatology" ed. by Mason,M. and Currey,H.L.F., 2nd edition, pitnam Medical,P.114.

Currey, H.L.F.,(1978):-

Aetiology and pathogensis of rheumatoid arthritis in "Copeman's textbook of The Rheumatic Diseases" (Ed.) Scott, J.T., Livingstone, London, New York, 5th edtition, P 261.

Dacie, J.V., and Lewis, S.M.,(eds)(1975):-

practical Haematology, 5th edition, Churchill-Livingstone-London.

Darby, P.W., (1953):-

Liver Function tests in rheumatoid arthritis. J.Clin. Pathol., 6:331.

Davis,P., and Hughes, G.R.V.,(1974):-

Singnificance of eosinophilia during gold Therapy. Arth. Rheum., 17:964.

De Gown,R.L.,(1967):-

Areview of The Therapeutic and hemolytic effects of dapsone. Arch. Int. Med., 120:242-248.

Deodhar,S.D., Pick, W.C., Hodgkinson, R. and Bachanan, W.W., (1973):-

Measurement of clinical respose to anti-inflammatory drug therapy in rheumatoid arthritis. Q.J.Med.New Series, 42:384-401.

Desilva,M., and Hazelman, B.L.,(1981):-

Long-term azathioprine in rtheumatoid arthritis adouble blind study. Annals of The Rheumatic Diseases. 40:560-563.

Dick,W.C., and Goodacre,J.,(1985):-

Rheumatoid arthritis. in Introduction of clinical Rheumatology. 2nd edition- English language Book Society/churchill Livingstone. 4:46-83.

Dickson,R.A. and Nicholle, F.V.,(1972):-

The assessment of hand function,part I measurement of individual digits. The hand: (4)3:207-214.

Dieppe, P.A., Doherty, M., Macfarlane, D., and

Maddison, P., (1985):-

"Rheumatological Medicine" churchill Livingstone. Edinburgh. London. Mebourne and New York. chap. 4 P. 41-64. chap 26:479-494.

Dingle, J., Horsfield, P., Fell, H. and Baratt, M., (1974):-

Breakdown of proteoglycan and collagen induced in pig articular cartilage in organ culture.. Ann. Rheum Dis. 34:303.

Dixon, A., St., J., (1971):-

The rheumatoid Foot. in :Modern trends in Rhoumatology 2" edited by Hill .A.G. Butterworths. London ch. 11 P. 158-173.

Dixon, J.S., Pickup, M.E., Lowe, J.R., Hallett, C., Lee, M.R., (1980):-

Discriminatory indices of response of patients with R.A.treated with D-penicillamine. ann. Rheum.. Dis.. 39:310-11.

Dixon , J.S., Bird , H.A., and wright, V., (1981):-

A comparison of serum biochemistry in ankylosing spondylitis. seronegative and seropositive rheumatoid arthritis ,Ann.Rheum .Dis 40 : 404

Dixkon, J.S., Hayes, S., Constable, P.D, L., and Bird, H.A., (1988):-

what are The "Best" measurements for montoring patiens during short-term second-line therapy? British Jaurnal of Rheumatology 27:37-43.

Downey, J.A., (1985)L:-

the physiatrist in Rheumatoid Arthritis Management from "Rehabilitation Management of Rheumatic conditions" 2nd ed. edited by Ehrlich. G.E., Williams Willins. Baltimore. London.

Duffy, J., Lidsky, M.D., and sharp, J.T., (1976):-

ployarthritis. polyarteritis and hepatitis B.. Medicine

.55:19

Duke, O., Panayi, G.S., Janossy, G., and poulter, L.w., (1982):-

An immunohistological analysis of lymphocyte subpopulations and Their microenvironment in The synovial membranes of patients with rheumatoid arthritis using monoclonal antibodies. clinical and Experimental Immunology, 49:22-30.

Duthie, J.J.R., Thompson, M., and Fletcher, W.B.(1955):-

Medical and Social aspects of The treatment of R.A. with special reference to factors affecting prognosis. Ann. Rheum. Dis. 14:133.

Duthie, R., and Harris, C., (1969):-

Aradiographic and clinical Survey of The hip joints in Seropositive rheumatoid arthritis. acta Orthopaedica Scandinavica 40:346.

Dyer, N.H., Kendal, M.H., and Hawkins, C.F.,(1971):-

Malabsorption in rheumatoid disease. Ann. Rheum. Dis.. 30:626-30.

Ehrlich, G.E., (1982):-

Heroic treatment for non-malignant disease. Journal of The American Medical Association. 248:1743-1744.

Elson, C.J., Scott, D.G.I., Blake, D.R., Bacon, P.A., and Holt, P.D.J., (1983):-

Complement-activating rheumatoid factor containing Complexes in patients with rheumatoid Vasculitis. Ann. Rheum. Dis.. 42:147.

Emonds, J. and Hughes, G., (1985):-

specific articular Manifestation in R.A. from "lecture Notes on Rheumatology. 1st ed. Blackwell scientific publications. Oxford. London. Edinburgh. Boston. paloalto, Melbourne. 7:41.

Ellis, H.A., and Felix-Davies, D., (1959):-

Serum Complement. rheumatoid factor. and other Serum proteins in rheumatoid disease and systemic lupus erythematosus. Ann. Rheum. Dis., 18:215-224.

Ellis, B.P., (1978):-

Leprosy and the rheumatoid factor. Cent. Afr. J. Med. 34:8-10.

Farr, M., Scott, D.L., Constable, T.J., Hawkins, C.F., and Stuart, J., (1983):-

Thrombocytosis of active rheumatoid disease. Annals of The Rheumatic Diseases. 42:545-549.

Fauci, A.S., (1985):-

Cytotoxic and other immunoregulatory agents from "textbook of Rheumatology" edited by Kelley. W.N.. Harris. E.D.. Ruddy. S.. and Sledge. C.B.. 2nd edition. Saunders Company. philadelphia. London. Toronto. Mexicocity. Riodejaneiro. Sydney and Tokyo. 55:833-857.

Feibel, A., and Fast, a., (1976):-

Deep heating of joints: Areconsideration. Arch. phys. Med. Rehab.. 57:513.

Feigenbaum, S.L., Masi, A.T., and Kaplan, S.B., (1979):-

Prognosis in rheumatoid arthritis: a longitudinl study of newly diagnosed younger adult patients. American Journal of Medicine. 66:377-384.

Fleming, A., Corwn, J.M., and Corbett, M., (1976):-

Early rheumatoid disease. I.Onset. Ann Rheum. Dis. 35:357.

Fleming, A., Benn, R.T., and Cordett, M., and Wood, P.H.M (1976,B):-

Early rheumatoid disease. II. Patterns of joint involvement. Ann. Rheum. Dis. 35:361-364.

Forster, P.J., Grindulis, K.A., Neumann, V., Hubball, S., and McConkey, B., (1982):-

high-dose intravenous methylprednisolone in

rheumatoid arthritis Annals of The Rheumatic Diseases. 41:444-446.

Fowler, P.D., Shadforth, M.F., Crook, P.R., and Lowton, A.,(1984):-

Report on chloroquine and dapsone in treatment of rheumatoid arthritis: a 6-month Comparative study. Ann. Rheum. Dis., 43:200-204.

Frangione, B., (1981):-

Immunologic aspects of inflammation: Immunoglobulin structure and function. In: "Textbook of Rheumatology" edited by Kelly. W.N., Harris. E.D., Ruddy. S. and sledge. C.B., Saunders Company. philadelphia. Vol. I. P.8.

Gardner, D.L., (1986):-

"Pathology rheumatoid arthritis" from Copeman's textbook of The rheumatic diseases edited by Scott. J.T., 6th ed Volume one. Churchill. Livingstone. Edinburgh. London. Melbourne. and New York 25:604-652.

Gather, R.A., and Richmond, J.D., (1975):-

Predominance of synovial fluid lymphocytes in early rheumatoid arthritis. J.Rheumatol. 2:340.

Gault, S.J., and Spyker, J.M., (1969):-

Beneficial effect of immobilization of joints in rheumatoid and related arthritis: a splint of study using sequential analysis. Arthritis and Rheum., 12:34.

Genant, H.K., (1985):-

Radiology of Rheumatic Diseases from "Arthritis and Allied conditions " edited by MeCarty. D.J..Hollander. J.L., 10th ed., Lea. febiger. philadelphia. 5:76-147.

Glick, E.N., (1967):-

Asymmetrical rheumatoid arthitis after poliomyelitis. Br. Med. J., 3:26.

Glynn, L.E., (1972):-

"Pathology, Pathogenesis and Aetiology of rheumatoid arthritis". Ann. Rheum. Dis.. 32:412.

Gohel, V., Dalinka, M.K. and Edeiken, J.,(1972):-

Giant rheumatoid Pseudocyst. Acase report. Clin. Orthop.. 88:151.

Gottlieb, N.L., Smith, P.M., and Smith, E.M., (1974):-

Pharmacodynamics of 195 Au labeled auriothiomalate in blood. Correlation. with Course of rheumatoid arthritis .gold toxicity and excretion. Arth x Rheum. 17:161.

Golding, D.N., (1978):-

Rheumatoid arthritis in "Synopsis of Rheumatic Diseases" Bristol. wright. J. and Sons LTD 3th ed.

Golding, D.N., (1982):-

Rheumatoid arthritis in:Synopsis of Rheumatic Diseases" Bristol. wright. J.and Sons LTD. 4th ed.

Grenan, D.M., Anderson, J.A., Kennedy, A.C., Mitchell, W., Dick, W.C., and Buchanan, W.W., (1975):-

Relation between Haemoglobin concentration and other clinical and laboratory parameters in R.A. Current Medical Research and opinion. 3:104.

Griffin, A.J., Gibson, T., Hustion, G.(1983):-

Acomparison of conventional and Low-dose sodium aurothiomalate treatment in rheumatoid arthritis. British Journal of Rheumatology. 22:82-88.

Grindulis, K.A., and McConkey, B.,(1982):-

The haematological effects of dapsone in R.A. In: Amos. R.s.. and Walker. D.F.. Immune Manpulation in Rheumatoid arthritis. 3:51

Grindulis, K.A., and McConkey, B., (1984):-

Outcome of attempts to treat rheumatoid arthitis with gold. penicillamine. Sulphasalazine ordapsone. Ann. Rheum. Dis.. 43:398-401.

Gumpel, J.M., (1978):-

Which anti-inflammatory drug in rheumatoid arthritis? Br. Med. J.. 2:56.

Gupta, P.J., (1970):-

R.A. : The Clinical Spectrum in "Textbook of Rheumatology" Edited by Kelly. W.N., Harris. E.D.. Ruddy. S. and Sledge. C.B.. Saunders Company. philadelphia. vol I. P. 928 (1981) Quoted by Harris. E.D.

Gupta, R.C., and Mills, D.M., (1975):-

Still's disease in adult:Alink between juvenile and adult rheumatoid arthritis. Am.J.Med. Sci. 269:137.

Haataja, K., and Kalliomaki, J.L.,(1978):-

Laboratory Scale for evaluating The activity of R.A.. Rheumatism and Rehabilitation. 17:83-85.

Halla, J.T., Koopman, W.J., Schrohenloner, R.E., Darby, W.L., and Heck, L.W., (1983):-

Local synthesis of Ig M. and Ig M rheumatoid factor in rheumatoid pleuritis. Journal of Rheumatology. 10:204-209.

Hall, A.P., (1975):-

The decision to operate in rheumatoid arthritis. Orthoped. Clin. North. Am.. 6.675.

Hall, R.P., Lawley, T.J., Smith, H.R., and Katz, S.I. (1982):-

Bullous eruption of systemic lupus erythematosus. Ann. Intern. Med.. 97:165.

Hart, H., McCormick, J.N. and Marmion, B.P. (1979):-

Viruses and lymphocytes in R.A. II. Examination of lymphocytes and Sera from patients with R.A. for evidence of retorvirus infection. Ann , Rheum. Dis.. 38:514-525.

Harkness, J.A.L., and Blake, D.R., (1982):-

Penicillamine nephropathy and iron. Lancet. ii. 1368-1370.

Harris, E.D., (1981):-

Pathogenesis of rheumatoid arthitis. In "Textbook of Rheumatology" edited by Kelly. W.N.. Harris. E.D.. Ruddy. S.. and Sledge. C.B.. Saunders company. philadelphia. Vol. 1 P. 896.

Harris, E.D., (1985):-

Rheumatoid Arthitis: The Clinical spectrum from "textbook of Rheumatology"edited by:Kelly. W.N.. Harris. E.S.. Ruddy. S. and sledge. C.B.. 2nd edition. W.B. Saunder 's Company philadelphia. London. Toronto. Mexicocity. Riode janeiro. Sydney and tokyo. 60:915-950.

Haslock, I., (1983):-

Report of The combined annual provincial meeting of The British Association for Rheumatology and Rehabilitation. The Herberden Society. The Royal Society of Medicine Section of Rheumatology and Rehabilitation and The Irish society of Rheumatology and Rehabilitation. British. Journal of Rheum. 22:57-58.

Haslock, D.I., Wright, V., and Harriman, S.G.F.,(1970):-

Neuromuscular disorders in rheumatoid arthitis. Amotor-point muscle biopsy. study. Q.J. Med.. 39:335.

Hayes, G.S., and Stinson, I.N.,(1976):-

Erthrocyte sedimentatioon rate and age. Arch. Ophthalmol.. 94:939.

Helin, H., Korpela, M., Mustonen, J., and Pasternack, A., (1986):-

Mild mesangial glomerulopathy with hematuria or proteinuria. Nephron. 42:224.

Heptinstall, R.H., (1983):-

Pathology of The Kidney. Little Brown and Company. Boston.

Hill, H.F.H., Hill, A.G.S., Day, A.T., Brown, R.M., Grolding, J.R., and Lyle, W.H., (1979):-

Maintenance dose of penicillamine in rheumatoid arthritis: a Comparison between a standard and aresponse-related flexible regimen. Annals of The Rheumatic Diseases. 38:429-433.

Holborow, E., (1978):-

Rheumatoid factors and antinuclear antibodies. In "Copeman's Textbook of The Rheumatic Diseases" edited by scott. J.T.. Livingstone. London. 5th ed. P.167.

Holland, C.D., Rennie, J.A.N., Hassan, I.F., Jasani, M.K., and Jayson, M.I.V., (1982):-

Extravascular (e-v) Fibrin in rheumatoid arthritis: persistence and Continuous turnover. annals of The rheumatic disease. 41:311.

Hollander, J.L., (1985):-

Arthrocentesis Technique and Intrasynovial Therapy In "Arthritis and Allied Conditions" edited by McCarty. D.J.and Hollander. J.L.. 10th.ed. Lea.Febiger philadelphia. 34:541-553.

Holt, L.P.J., (1986):-

Rheumatoid Arthritis from "Therapeutics in Rheumatology" edited by Moll. J.M.H.. BIRD. H.A.. and Rushton. A.. London. CHAPMAN and HALL. 11:321-357.

Honkanen, E., Tornroth, T., Pettersson, E., and Skrifvars, B., (1987):-

membranous glomerulonephritis in R.A. not related to gold or D-penicillamine Therapy: areport four Cases and review of The Literature. Clin Nephrology 27:87.

Hughes, G.R.V., and Currey. H.L.F.(1975):-

Laboratory investigation. In "An introduction of

Clinical rheumatology" edited by Mason. M.. pitnam Medical. P. 348.

Hull, S., and Mathews, J.A., (1982):-

Pulmonary necrobiotic nodules as a presenting features of rheumatoid arthritis. Annals of The Rheumatic Diseases. 41:21-24.

Hunder, G. and Mc. Duffie, F., (1973):-

Hypocomplementaemia in rheumatoid arthritis. Am.J. Med.. 54:461.

Hurd, E.R., and Cheatum, D.E., (1976):-

Decreased spleen size and increased neutrophils in patients with felty's syndrome. Effects of gold sodium Thiomalate Therapy. JAMA.. 235:2215-2217.

Huskisson, E.C.,Sturrock, R.D., and Tugwell, P.,(1983):-

Measurement of patient outcome Br.J.Rheum. 22(suppl) 86-89.

Huskisson, E.C.(1986):-

"Clinical Trials and Therapeutic evaluation" from copeman's textbook of The Rheumatic Diseases edited by Scott. J.T.. 6th ed. volume two. Melbourne. and New York 65:1581-1596.

Jacoby, R.F., Jayson, M.I.V., and Cosh, J.A., (1973):-

Onset. Early stages. and prognosis of rheumatoid arthritis. Aclinical study of 100 patients with 11-year follow-up. British medical journal. 2:96-100.

Janossy, G., Panayi, G.S., and Duke, O., (1981):-

Rheumatoid arthritis: adisease of T-lymphocyte / macrophage immunoregulation. lancet 2:839-842.

Johansson, S.V. and Stranlberg, P.O., (1972):-

Haem biosynthesis studied in patients with rheumatoid arthritis. J. Clin. pathol.. 25:159-162.

Jordan, J.D., and Snyder, C.H., (1964):-

Rheumatoid disease of The lung and Cor pulmonale.

American Journal of Diseases of childhood. 108:174.

Katz, S.I., Gallin, J.I., Hertz, K.C., Fauci, A.S., and lawley, T.J., (1977):-

Erythema elevatum diutinum : Skin and systemic manifestations. immunologic studies and successful Treatment with dapsone. Medicine. 56:443.

Katz, W.A., (1985):-

Rheumatoid Arthritis In "Rheumatic Therapeutics" edited by Roth. S.H.. Calabro. J.J.. Paulus. H.E. and Willkens. R.F.. McGraw-HillBook Company. New York. 1:3-18.

Kammermann, J.S., (1966):-

Protective effect of traumatic lesions on rheumatoid arthritis.. Ann. Rheum. Dis.. 25:361.

Kampner, S.L., and Kuzell, W., (1976):-

intra-articular rheumatoid nodule of The Knee joint. Clinical orthopaedics and Related Research. 114:243-247.

Kantor, T.G., (1982):-

Control of pain by non-steroidal anti-inflammatory drugs. Med. Clinics N.Am.. 66:1053-1059.

Kay, R.L., and Hammond, A.H., (1978):-

Understanding rheumatoid arthritis. Evaluation of apatient education program. JAMA. 239:2466.

Kean, W.F., and Anastassiades, T.P., (1979):-

Long term chrysotherapy. Incidence of toxicity and efficacy during sequential time periods. Arthritis and Rheumatism. 22:495-501.

Kean, W.F., Dwosh, I.L., Anastassiades, T.P., Ford, P.M., and Kelly, H.G., (1980):-

The toxicity pattern of D-penicillamine Therapy: Aguide to its use in rheumatoid arthritis. Arthritis and Rheumatism. 23:158-164.

Bioavailability and pharmacokinetics of D-penicillamine. J.Rheumatol.. 10:90-94.

Kushner, I.(1981):-

The acute phase reactants and The E.S.R. In "Textbook of Rheumatology". Edited by Kelly. W.N. Harris. E.D.. Ruddy. S.. and Sledge. C.B.. Saunders Company. philadelphia. Vol.1.P.672.

Laursen, M.C., (1978):-

The influence of Salicyl-azosulphapyridine on The immune response to antigenic tumour cells innoculated into The coecal luman of C3 H mice. Scandinavian Journal kof Gastroenterology. 13:199-997.

Lea, A.L., (1964):-

Articular and systemic manifestations of R.A. from :Copeman's textbook of The Rheumatic Diseases" edited by Scott. J.T.. 6th edition. volume. one.. Churchill. Livingstone. edinburgh. London. Melbourne. and New York.. P.690. (1986)

Quoted by Buchanan. W.W.. and Kean. W.F.

Leftkovits, A.M., and Farrow, I.J., (1955):-

The Liver in rheumatoid arthritis. Ann. Rheum. Dis 14:162-169.

Lightfoot, R.W., (1985):-

Treatment of Rheumatoid arthritis from "Arthritis and Allied Conditions" edited by McCarty. D.J. Hollander. J.L.. 10th ed. Lea. febiger. philadelphia. 42:668-676.

Ligumsky, M., Rachmilewitz, D., and zor, U., (1978):-

Role of Prostaglandins in ulcerative Colitis. Enhanced production during activ disease and inhibition by sulphasalzine. Gastroenterology 75:638-640.

Lindjberg, I.F., (1964):-

Juvenile rheumatoid arthritis: Afollow-up of 75 cases. Arch. Dis. child.. 39:576-583.

Littler, J.W., and Eaton, R.G. (1967):-
Redistribution of forces in The Correction of The boutonniere deformity. Journal of Bone and joint Surgery, 49A:1267.

London, M.G., Huirden, K.D., and Hewitt, J.V., (1963):-
Serum cholesterol in rheumatic diseases. Br.Med.J.. 1:1380-1383.

Lorber, A., Simon, T.M., Leeb, J., Peter, A., and Wilcox, S.A., (1979):-
Effect of chrysotherapy on parameters of immune response. the Journal of Rheumatology. 6.. Suppl. 5.82.

Lorber, A., Kunishima, D.H., Harralson, A.F., and Simon, T.M., (1983):-
II. Unbound versus total serum gold concentration. pharmacological action on cellular function. J.Rheumatol.. 10-568-573.

Luukkainen, R., Isoinaki, H., and Kajander, a.,(1983):-
Prognostic value of the Type of onset of R.A.. Ann. Rheum. Dis.. 42:274-275.

Mac farlane, J.D., and Van der linden S.J.(1981):-
Leaking rheumatoid olecranon bursitis as a Cause of forearm Swelling. Annals of The Rheumatic Diseases 40:309-311.

Mackenzie, A.H., (1983):-
Dose refinements in long-Term therapy of rheumatoid arthritis with antimalarials. Am.J.Med.. 75:40-45.

Maddin, S.,(1985):-
Dermatologic Therapy from "Dermatology" 2nd ed. Volume 2 . edited by Moschella. S.L.. and Hurley. H.J.. W.B.. Saunders company. philadelphia London.

toronto. Mexicocity. Riode janeiro. Sydney and Tokvo. P:1971-1972.

Malmquist, E., and Reichard, H.,(1962):-

Serum ornithine carbamoyl transferase and Transaminase activity in rheumatic disease. Acta rheumatol. Scand.. 8:170-182.

Mandell, G.L., and Sande, M.A., (1980):-

Antimicrobial agents: Drugs used in The chemotherapy of Tuberculosis and leprosy In Goodman and Gilman's. The pharmacologic Basis of Therapeutics. edited by Gilman. A.G.. Goodman. L.S.. and Gilman. A.. 6th ed. New York. Macmillan comp. 53:1200-1221.

Mandell, G.L. and Sande, M.A., (1985):-

Antimicrobial agents: Drugs used in The chemotherapy of Tuberculosis and leprosy. In Goodman and Gilman's. The pharmacologic Basis of Therapeutics. edited by Gilman. A.G.. Goodman. L.S.. Rall. T.W. and Murad. F.. 7th ed. Macmillan publishing company. New york. Toronto. London. 53:1199-1218.

Mancini, G., Carbonara AE, and Heremans, J.F., (1965):-

Immunochemical quantitation of antigens by single radial immunodiffusion. Immunochemistry. 2:235.

Marcolongo, R.,Bayeli, P.F.,and Moontagnani, M.,(1979):-

Gastrointestinal involvement in rheumatoid arthritis abiopsy study. Journal of Rheumatology 6:163-173.

Marks, J.S., (1982):-

Chloroquine retinopathy: is there a safe daily dose? Ann. Rheum. Dis. 41:52-58.

Marshall, R.N., Myers, D.B., and palmer, D.G., (1980):-

Disturbance of gait due to rheumatoid disease. Journal of Rheumatology 7:617-623.

Matrel, W., Holt, J.F., and Cassidy, J.T., (1962):-

Roentgenologic manifestations of iuvenile rheumatoid

arthritis, Am.J.Roentgenol.. 88:440.

Martel, W., Hayes, J.T., and Duff, I.F., (1965):-

The pattern of bone erosion in The hand and wrist in R.A.. Radiology. 84:204.

Martineck, R.G., (1964):-

J.Amer Med. Technol. 26:551..Quoted from practical clinical Biochemistry, vol 1.5th ed.. Varley. H.. Gowenlock. A.H.. and Bell. M.. Eds.. William Heinemann Medical Books LTD London. P. 457.1980.

Mason, M. and Barnes, C., (1975):-

Rheumatoid arthritis in "An introduction of Clinical Rheumatology" (Ed.) Mason. M and currey. H.. Pitnam. London. 2nd edition

Mastaglia, G.L., and Owen, E.T., (1981):-

astudy of The response of The leukopenia of rheumatoid arthritis to gold salt therapy.J.Rheumatol. 8:658.

Mathews, J.A., (1969):-

Atlanto-axial subluxation in rheumatoid arthritis. Annals of The Rheumatic Diseases 28:260.

McCarty, D.J., and Hogan, J.M., (1964):-

Inflammatory reaction after intra-synovial injection of microcrystalline adrenocorticosteroid esters. Arthritis x Rheum. 7:359.

McCarty, D.J., and Gatter, A.A., (1966):-

Astudy of distal interphalangeal joint Tenderness in rheumatoid arthritis.Arthritis and Rheumatism.9:325.

McCarty, D.J., (1979):-

Clinical assessment of arthritis. In "Arthritis and allied Conditions" ed. by McCarty. D.J.. Hollander. J.. 9th ed.. Lea Febiger. philadelphia p.131-147.

McCarty, D.J., (1985):-

"Synovial fluid" In Arthritis and allied Conditions" edited by McCarty. D.J.. and Hollander. J.L.. 10th ed.. Lea. Febiger. philadelphia 4:54-75.

McConkey, B., Davies, P., and Crockson, R.A., (1976):-

Dapsone in rheumatoid arthritis. Rehabil.15:230-234.

McConkey, B., Davies, P., and Crockson, R.A., (1979):-

Effects of gold ,dapsone .and prednisolone on serum-c-reactive protein and haptoglobin and the erythrocyte sedimentation rate in rheumatoid arthritis. Ann. Rheum.Dis.. 38:141-144.

McConkey, B., Amos, R.D., and Durham, S., (1980):-

Sulphasalazine in rheumatoid arthritis. Br.Med. J.. 280:442-444.

McCormick, J.N., (1963):-

An immunofluorescence study of rheumatoid factor Ann. Rheum. Dis. 22:1.

McGinty, J.B., (1985):-

Arthroscopy: In "Textbook of Rheumatology"edited by Kelly. W.N.. Harris. E.D.. Ruddy. S. and sledge. C.B.. 2nd ed. Saunders Company. piladelphia London. Toronto. Mexicocity. Rio de janeiro. Sydney. and Tokyo.41:640-648

McGuire, J.L. and Harris, E.D.(1979):-

Clinical presentation and Course of R.A. in Rheumatology and Immunology (ed. by A.S.Cohen) Grune and stratton. Inc. P. 180-187.

McKenna, F.,(1988):-

Clinical and laboratory assessment of outcome in Rheumatoid Arthritis. British Journal of Rheumatology. 27(suupl 1) : 12-20.

Meijer, K.A.., Van Beusekon, G.TH., Luyendijk, W., and

Duijfjes, F., (1974):-

Dislocation of The Cervical spine with cord compression in R.A..J.Bone joint surg. (Br.). 56:668.

Mexfield, W.S., Weiss,T.E., and Shuler,S.E., (1972):-

Synovial membrane Scanning in arthritic disease from "Arthritis and allied conditions " edited by McCarty. D.J..X Hollander.J.L.. 10th ed.. Lea.febiger philadelphia.p708(1985)

Quoted by Genant, H.K.

Miller, B., Demerinex, P., and Srinivasan, R.,(1980):-

Double blind placebo controlled cross-over evaluation of Levamisole in rheumatoid arthritis. Arthritis Rheum. 23:172-182.

Moens, C., and Broeckaert,J.,(1985):-

treatment of rheumatoid arthritis with immunosuppressive drugs. Acta Rheumatologia Scandinavica. 11:212-220.

Moll, J.M.H., (1987):-

Joints affected in R.A.. from Rheumatology in Clinical practice 1sted.. Blackwell scientific publications oxford. London. Edinburgh . Boston . Paloalto. and Melbourne. 12:312-314.

Mongan, E.S., (1969):-

Laboratory findings in rheumatoid arthritis "serum complement" from Arthritis and allied conditions edited by MaCarty. D.J.. Hollander. J.L.. 10th edition.. Lea. Febiger, philadelphia. P.650.1985.
Quoted by Baum. J. and Ziff. M..

Moschella, S.L., (1985):-

Diseases of The mononuclear phagocytic system (The So-called Reticuloendothelial system). In "Dermatology" 2nd ed. Vol(1) edited by Moschella. S.L.. and Hurley. H.J.. W.B. Saunders copmay. philadelphia. London. Toronto. Mexicocity. Riodejaneiro. Sydney. and Tokyo. P. 971.

Mowat, A.G., (1978):-

surgical Treatment of rheumatoid arthritis. In "copeman's textbook of The Rheumatic Diseases". edited by Scott. J.T.. 5th edition. NewYork.

Churchill livingstone. P. 459.

Mueller, M.N., and Jurist, J.M., (1973):-

Skeletal status in rheumatoid arthritis. Arthritis and Rheumatism. 16:66.

Multicentre study group (1982):-

Levamisole in rheumatoid arthritis Ann. rheum. Dis. 41:159:163.

Munthe, E., (1978):-

Deposition of immune complexes in synovial membrane and fluid in : Panayi. G.S., and Johnson. P.M.(eds) Immunopathogenesis of rheumatoid arthritis. Reed Books. chertsey. P. 85-88.

Namey, T.C., (1985):-

Nuclear Medicine. and special Radiologic Imaging Techingue in The Diagnosis of Rheumatic diseases: from "textbook of Rheumatology" edited by Kelly. W.N., Harris. E.D., Ruddy. S.and sledge. C.B., 2nd edition. Saunders company. philadelphia. London. Toronto. Mexicocity. Riodejaneiro. sydney. and Tokyo 40:608-640.

Nissila, M., Nuotio,P., Von Essen, R., and Makisara, P., (1982):-

Low dose penicillamine treatment of rheumatoid arthritis. Comparison of 600 mg. and 300 mg. regimes. Scand. J. Rheumatol., 11:161-164.

Nived, O., Styrfell, G., Westting, H., and White, T., (1983):-

Is serum creatinine concentration a reliable index of renal function in rheumatic diseases?
Br. Med. J., 286:684-685.

Nosanchuk. J.S., and Schnitzer, B.,(1969):-

Follicular hyperplasia in Lymph nodes from patients. with R.a., Cancer. 24:343.

Notman, D.D., Kurata, N., and Tan, E.M., (1975):-

Profiles of antinuclear antibodies ' in systemic rheumtic disease. Ann. Intern. Med., 83:464.

Nusinow, S., and Arnold, W.J., (1982):-

Prognostic value of c-reactive protein (CRP) levels in rheumatoid arthritis. Arthritis x Rheum. 25:524.

O,Driscoll, S., and O'Driscoll,M., (1980):-
Osteomalacia in rheumatoid arthritis. Ann. Rheum.. Dis.. 39:1.

Ognibene, A.J., (1970):-
Agranulocytosis due to dapsone. Ann. Inter. Med. 73:521-4.

Panayi, G.S., Wooley,P.,and Batchelor,J.R.,(1978):-
Genetic basis of rheumatoid disease :HLA antigens. disease manifestations and toxic reactions to drug. British medical journal. 2: 1326-1328

Panayi,G.S.,(1982):-
Scientific Basis of Rheumatology. Churchill Livingstone Edinburgh London. Melbourne NewYork. P. 61-130.

Panayi, G.S., and David, C.(eds)(1983):-
Clinical immunology I: Immunogentics. Butterworths. London.

Panayi, G.S.,(1986):-
The aetiopathogenesis of rheumatoid arthritis from Copeman's Textbook of The Rheumatic Diseases Edited by Scott. J.T. 6th edition Volume one. CHURCHILL. Linigstone.Edinburgh. London. Melbourne. and New York. 24:595-603.

Panush, R.S., Franco, A.E. and Schur, P.H.,(1971):-
Rheumatoid arthritis associated with eosinophilia Annlas of Internal Medicine. 75:199.

Paradis, G.R., and Kelly, P.J., (1975):-
Blood flow and mineral deposition in Canine tibial fractures. J.Bone. Joint surg.. 57A:220-226.

Partridge, R.E.H., and Duthie,J.J.R., (1963):-
controlled Trial of The effects of Complete immobilization of The joints in rheumatoid arthritis. Ann. Rheum. Dis. 22:91-99.

Patterson, C.D.,Harville, W.E.,and Pierce. J.A.,(1965):-
Rheumatoid lung disease. Annals of Interal Medicine 62:685.

Paulus, H.E., Machleder, H.I., Levine,S.Yu,D.T.Y., and MacDonald,N.S., (1977):-
Lymphocyte involvement in rheumatoid arthritis.

Studies during Thoracic duct drainage. Arthritis x Rheum. 50:1249-1262.

Person, D.A., Sharp, J.T., and Rawls, W.E., (1973):-

Attempts to identify Viruses and mycoplasmas in Connective Tissue diseases.. Arthritis x Rheum. 16 : 125.

Phillips. P.E., (1982):-

Infection and the pathogenesis of Connective tissue diseases . in Panayi. G.S.. (ed):
Scientific basis of Rheumatology. Edinburgh. Churchill-Livingstone .

Pickup, M.E., Dixon, J.S., Hallett, C.Brid, H.A., and wright V.,(1981):-

Plasma Viscosity-anew appraisal of its use as an index of disease activity in rheumatoid arthritis . Ann Rheum .Dis .. 40 : 272-275.

Popert, A.J., Scott, D.L., Wainwright, A.C., Walton, K.W., Williamson, N., and chapman, J.H., (1982):-

Frequency of occurrence, mode of development and significance of rice bodies in rheumatoid joints . Annals of the rheumatic diseases. 41:109-117.

Poulter, L.W., Duke, O., and Hobbs, S., (1983):-

the involvement of interdigitating (antigen-presenting) cells in the pathogenesis of rheumatoid arthritis. clinical and experimental immunology. 51:247-254

Pullar, T., Hunter, J.A., and Capell, H.A., (1983):-

Sulphasalazine in rheumatoid arthritis : a double blind comparison of sulphasalazine with placebo and sodium aurothiomalate. Br. Med.J.. 287:1102-1105

Radin, E.L., Ehrlich, M.M., Weiss, C.A., and Parker, H.G., (1976):

Pathology of rheumatoid arthritis. In "Copeman's Textbook of The Rheumatic Diseases "edited by Scott. J.T.. Livingstone. London. NewYork. 5th edition P. 273(1978): Quoted by Gardner. D.L.

Ranawat, C.S., and Straub, L.R., (1970):

Volar Tenosynovitis of wrist in rheumatoid arthritis. Arthritis and Rheumatism 13:112

Rapoport, A.M., and Guss, S.B., (1972):

Dapsone-induced peripheral neuropathy. Arch. Neurol. 27:184-186.

Rasbridge, M.R., and scott, G.L., (1973): The haemolytic action of dapsone: changes in The red cell membrane. Br.J. Haematol: 24:183-93.

Rask, M.R., (1978):

Achilles tendon rupture owing to rheumatoid disease. JAMA 239:435.

Razzano, C.D., wilde, A.H., and, Phalen, G.S., (1973):

Bilateral rupture of The infrapatellar Tendon in R.A., Clin. orthop, 91:158.

Rhind, V.M., Bird, H.A., and Wright, V., (1980):

Acomparison of clinical assessments of disease activity in rheumatoid arthritis. Ann. Rheum. Dis.. 39:135-137.

Rhodes, K., Scott, A., and Markham, R.L., (1969):

Immunological sex differences: a study of patients with R.A.. Their relatives and controls. Ann. Rheum. Dis. 28:104.

Ritchie, D.M., Boyle, J.A., and McInnes, J.M., (1968):

Clincal studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Quarterly Journal of Medicine. 37:393-406.

Ropes, M.W., Bennett, G.A., Cobb, S., Jocox, R. and Jessar, R.A., (1959):
Diagnostic criteria for rheumatoid arthritis. 1958 Revision . Ann. Rheum. Dis.. 18:49-53.

Rosenthal, M., trabert, U., and Mueller, W., (1976):
Cytotoxic and other immunoregulatory agents from "Textbook of Rheumatology" edited Kelley,W.N.. Harris E.D.. Ruddy, S.. and sledge, C.B.. 2nd edition. W.B.,Saunders company. Philadelphia. London. Toronto. Mexicocity. Riodejaneiro. Sydney. and Tokyo. P. 849(1985) Quoted by fauci, A.S.

Rubin, E.H., Gordon, M, and Thelmo, W.L., (1967):
Nodular pleuropulmonary rheumatoid disease. American Journal of Medicine. 42:567.

Ruddy, S., (1985):
The Management of Rheumatoid Arthritis from "Textbook of Rheumatology" edited by Kelley, W.N.. Harris. E.D.. Ruddy. S., and sledge. C.B.. 2nd edition.W.B.. Saunders company. philadelphia. London. toronto. Mexicocity. Riodejaneiro. sydney. and Tokyo 63:979-992.

Sahad, M.a., and Cohen, R.J., (1971):
Effect of aspirin ingestion on ascorbic-acid levels in rheumatoid arthritis. Lancet. 1:937-938.

Sakane ,T., Takada, s., and Murakawa, y., (1982):-
Analysis of suppressor"T" cell function in patient with rheumatoid arthritis .J.Immunol.. 129: 1972-1977

Schumacher, H.R., (1982):
Palindromic onset of rheumatoid arthritis. Arthritis x Rheum. 25:361.

Schumacher, H.R., (1985):
Synovial fluid analysis\synovial biopsy.In "textbook of Rheumatology" edited by Kelley. W.N.. Harris. E.D.. Ruddy. S.. and sledge. C.B.. 2nd ed.. W.B. Saunders compnay philadelphia. London. Toronto. Mexicocity.

Riodejaneiro, syndney, and tokyo. 38:561-568. 42:648-653

Scott, J.T., (1960):
Morning stiffness in rheumatoid arthritis. Ann. Rheum. Dis., 19:361.

Scott, D.L., Symmons, D.P., and coulton, B.L., and Popert, A.J., (1987):
Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet: 1:1108-1115.

Seah, P.P., Fry, L., Mazaheri, M.P., Mowbray, J.F., Hoffbr AND, A.V., and Holborow, E.J., (1973):
"Alternate-pathway Complement fixation by IgA in the skin in Dermatitis Herpetiformis" Lancet, ii, 175.

Seifert, M.H., (1983):
Rheumatoid arthritis and Related diseases: clinical aspects. from postgraduate textbook of clinical orthopaedics edited by Harris,N.H,and wright P.S.G., Bristol London. Boston 17:457.

Shapiro, J.(1970):-
Anew factor in the etiology of ulnar drift. Clinical orthopaedics 68 : 32

Shapiro, S., Siskind, V., Mosson, R.R., Heinonen, O.P., Koufman, D.W., and Slone, D., (1976):
Perinatal mortality and birth weight in relation to aspirin taken during pregnancy, Lancet. 1:1375-1376.

Shapiro, R., Weisner, K., Mclaughlin, G.W., and Utsinger, P.D., (1985):
Evaluation as aprelude to Management; Management of patients. In Rheumatoid Arthritis Etiology. Diagnosis. Management "edited by Utsinger. P.D., Zvaifler. N.J., and Ehrlich. G.E.. J.B.. lippincott company philadelphia. London. Mexicocity x NewYork 32:505-544.

Sharp, J.T., Lidsky, M.d., and Duffy, J., (1982):
cinical resposes during gold therapy for rheumatoid arthritis: changes in synovitis. radiologically

detectable erosive lesions. serum proteins and serological abnormalities. Arthritis and Rheumatism. 25:540-549.

Shepard, C.C., Ellard, G.A., Levy,L., Upromolla, V.,Pattyn, S.R., Peters, J.H., Rees, R.J.W., and Waters, M.F.R., (1976):

Experimental chemotherapy of leprosy.

Bull. WHO, 53:425-433.

Shiokawa, Y., Horiuchi Y., Houma, M., Kageyama, T., Akada, T., and Azuma, T., (1977):

Clinical evaluation of D-penicillamine by multi-centric double-blind study in chronic rheumatoid arthritis. Arthritis and Rheumatism. 20:1464-1472.

Shiozawa, S., and Ziff, M., (1983):

Immunoelectron microscopic demonstration of fibronectin in rheumatoid pannus and at the cartilage-pannus junction. Annals The rheumatic Diseases. 42:254-263.

Sigler, J.W., Bluhm, G.M., Duncan, H., Sharp, J.T., Ensign, D.C., and McCrum, W.R., (1974):

Gold salts in The treatment of rheumatoid arthritis. Annals of Internal Medicine. 80:21-26.

Slone, D., Siskind, V., Heinonen, P.H., Monson, R.R., Kaufman, D.W., and Shapiro, S., (1976):

Aspirin and congenital malformations. Lancet. 1:1373-1375.

Snyderman, R., and Pike, M.C., (1978):

Pathophysiologic aspects of leukocyte chemotaxis Identification of a specific chemotactic factor binding site on human granulocytes and defects of macrophage fuction associated with neoplasia in "leukocyte chemotaxis: Methods, physiology and clinical Implication" edited by Gallin, J.I., and Quie, P.G., NewYork. Raven Press . 1978.

Smith, P., Benn, R.T. and Sharp, J., (1972):

Natural history of rheumatoid cervical luxations. Ann. Rheum. Dis.. 32:432.

Smollen, J.S., Menzel, E.J., and Scherak, O., (1980):

Lymphocyte transformation to denatured type I collagen and B lymphocyte alloantigens in rheumatoid Arthritis. Arthritis and Rheumatism. 23:424-431.

Solinger, A.M., Bhatnagar, R., and Stobo, J.D., (1981):

Cellular molecular and genetic characteristics of T cell reactivity to Collagen in man. Proceedings of The National Academy of Sciences, (USA).78:3877-3881.

Solinger, A.M., and Stobo, J.D., (1982):

Immune response genes control reactivity in man: collagen unresponsiveness in HLADR4 negative unresponders is due to the presence of T-dependent suppressive influences. Journal of Immunology. 129:1916-1920.

Sokoloff, L., (1974):

The pathology of rheumatoid arthritis and allied disorders in "arthritis and allied conditions ed by Hollander. J.. and McCarty. D. 8th edition. lea and febiger. NewYork. P.309.

Sorensen, A.W.S., (1961):

Investigations of The Kidney function in rheumatoid arthritis. II. acta Rheumatol. Scand.. 7:138-144.

Stastny, P., (1978):

Association of the B-Cell alloantigen DRW4 with rheumatoid arthritis. New England journal of Medicine 298:869-871.

Steinberg, A.C., and Wilson, J.A., (1963):

Hereditary globulin factors and Immune Tolerance in man. Science. 140:303.

Steinbrocker, O., Traeger, C.H., and Batterman, R.C.,(1949):

Therapeutic criteria in rheumatoid arthritis. J.A.M.A.. 140:659-662.

Stewart, S.M., Alexander, W.R.M., and Duthir, J.J.R.,(1969):

Isolation of diphtheroid bacilli from synovial

membrane and fluid in rheumatoid arthritis. Ann. Rheum. Dis.. 28:477.

Sullivan, S., Hamilton, E.B.D., and Williams, R., (1978):
Rheumatoid arthritis and Liver involvement. Journal of The Roval college of physicians (London). 12;416-422.

Sweetnam, D.R., Mason, R.M. and Murray, R.O., (1960):
Steroid arthropathy of The hip.British Medical journal i:1392.

Swezey, R.L., (1967):
Myocardial infarction due to rheumatoid arthritis.
JAMA. 199-191.

Swezey, R.L., (1986):
"Articular and Svstemic manifestations of rheumatoid arthritis" in Copeman's textbook of The Rheumatic Diseases edited by Scott. J.T..6th edition volum one. Churchill Livingstone. Edinburgh. London. Melbourne and NewYork. P.664

Swinson, D.R., Hamilton, E.B.O., Mathews, J.A. and Yates, D.A.H., (1972):
Vertical subluxation of The axis in rheumatoid arthritis.Annals of The Rheum. Diseases 31:359.

Swinson, D.R., Zlosnick, J., and Jackson, L., (1981):
Double-blind Trial of dapsone against placebo in The Treatment of Rheumatoid Arthritis. Ann. Rheum. Dis.. 40:235-239.

Tan, E.M., (1979):
The possible role of E.B.V. in R.A.. Review of infectious Diseases. 1:997-1005.

Tannenbaum, H., and Schur, P., (1974):
The role of lymphocytes in rheumatic diseases. J. Rheumatol.. 1:392-412.

Tarr, K.H., (1974):

Spontaneous rupture of Tendons in rheumatoid arthritis. New Zealand Medical journal. 79:651-563.

Thayer, M., Charland, C., and Field, C., (1976):

Salazopyrin and its effect on lymphocyte subpopulations and function. Gastroenterology. 75:638-640.

Theofilopoulos, A.N., burtonboy, G., lospalutto, J.J. and Ziff, M., (1974):

Ig "M"rheumatoid factor and low molecular weight Ig"M".An association with Vasculitis. Arth. x Rheum.. 17:272.

Thomas, A.R., Robinson, W.A., boyle, D.J., Day, J.F., Entringer, M.A., and steiger-wald, J.F., (1983):

Long Term effects of cyclophosphamide on granulocyte colony formation in patients with rheumatoid arthritis. J.Rheumatol.. 10:778-783.

Thompson, M.,(1965):

Progress in clinical rheumatology edited by Dixon. A. st.J.. Churchill. London, P. 10-26.

Thompson, M., (1966):

Non-articular features of rheumatoid disease In "Modern trends in rheumatology" ed. by Hill. A.G.S.. part1: P.32.

Tietz, N.W., (1970):

fundamentals of clinical chemistry, 1st ed.. W.B.. Saunders Company philadelphia. London, P.447.

Tomey, J.J., Rossen, R.D., Lewis, V.M., Laughter, A.H., and Douglass, C.C., (1976):

Rheumatoid Factor in "Textbook of Rheumatology" edited by Kelley. W.N.. Harris. E.D.. Ruddy. S.. and sledge. C.B.. 2nd edition. W.B. Saunders company philadelphia, London. Toronto. Mexicocity. Rio dejaneiro. sydney. and Tokyo ch:44. P.667 1985. Quoted by Carson. D.A.

Townes, m A.S., Sowa, J.M., and Shulman, L.E., (1976):

Controlled Trial of cyclophosphamide in rheumatoid arthritis. Arthritis x Rheum., 19:563-573.

Traycoff, R.B., Pascual, E. and Schumaker, H., (1976):
Mononuclear cells in human synovial fluid.
Arth x Rheum.. 19:743.

Uehlinger, E., (1971):
Bone changes in rheumatoid arthritis and Their pathogenesis in "Rheumatoid arthritis" ed. by Muller, W.. Harwerth. H.G. and Fehr. K.. Academic press, London and New york. P.25.

Unger, A., Kay, A., Griffin, A.J., and Panayi, G.S., (1983):
Disease activity and pregnancy-associated z-glycoprotein in rheumatoid arthritis during pregnancy. British Medical journal 286:750-752.

Utsinger, P.D., Zvaifler, N.J. and Ehrlich, G.E., (1985):
Etiology and pathogenesis from Arthritis (Aetiology. Diagnosis. Management). Company. philadelphia. London. Mexicocity. NewYork 3:21-48.

Vernon-Roberts, B., (1985):
Applied anatomy of joints in :"An introduction to clinical Rheumatology" edited by Mason. M., and Currey. H.L.F.. Pitnam medical. 2nd edition. P.1.

Vigidal, E., Jacoby, R., Dixon, A. st.J., Rattiff, A.H., and Kirkup, J.,(1975):
"The foot in chronic R.A."
Ann. Rheum. Dis.. 34:292.

Wagner, T. and Abgarowiez, T. (1970):
Microscopic appearance of Baker's cyst in cases of rheumatoid arthritis. Rheumatologia. 8:21-26.

Walker, W.C., and Wright, V., (1968):
Pulmonary lesions and rheumatoid arthritis. Medicine. (Baltimore) 47:501.

Walsh, L., Davis, P., and Moconkey, B., (1979):
Relationship between erythrocyte sedimentation rate and serum c-reactive protein in rheumatoid arthritis. Ann. Rheum. Dis. 38:362-363.

Ward, J.R., Williams, H.J., Eggar, M.J., and Reading, J.C., (1983):
Comparison of auranofin. gold sodium Thimalate and

placebo in The Treatment of rheumatoid arthritis. a Controlled clinical Trial. Arthritis & Rheum.. 26:1303-1315.

Watson, R.G., (1965):

Amore specific methed for detecting and quantitating rheumatoid factors using a simple modification of The RA. Test. Am. J.Clin. Pathol. . 43.152.

Webb, J. and Payne, W.H., (1972):

Rheumatoid nodules of The vocal folds. Annals of The rheumatic Diseases 31:122.

Webb, J., Whaley, K., MacSween, R.N.M., Nuki, G., Dick, W.C., and Buchanan, W.W., (1975):

Liver disease in rheumatoid arthritis and sjogren's syndrome. Propective study using biochemical and serological markers of hepatic dysfunction. Annals of The Rheumatic Diseases. 34:70.

Wegelius, D., Wafin, F., Falck, H., and Tornroth T., (1979):

Follow up study of amyloidosis secondary to rheumatic disease. In: Proceedings of The Third international symposium on amyloidosis,Glenner. G.G.. Costa. P.P.. and Freitas. A.F.. Eds. Excerpta Medica. Amesterdam P:183.

Weinstein, A., Peters, S., Bronn, S., and Bluestone, R., (1972):

Metabolism of The third component of Complement (C3) in patients with rheumatoid arhtritis.. Arthritis x Rheum. 15:49.

Weiss, J.J., thompson, G.R., Doust, V., and Burgener, F., (1975):

Rotator cuff tears in R.A.
Arch.Intern. Med. 135:521.

Whaley, K., Williamson, J., chishol , D.M., Webb, J.Mason, D.K. and Ruchanan, W.W., (1970):

Liver disease in sjogren's syndrome and R.A. Lancet. 1:861-863

Weissberg,E.L., Resnick,D.,and taylor,A.,(1978):-

R.A. and its variants analysis of radiographic and clinical

examination ,Am J. roentgenol.. 131 : 665.

Wiik, A., and Munthe, E., (1974):

Complement-Fixing granulocyte-specific antinulcear factors in neutropenic Cases of rheumatoid arthritis. Immunol.. 26:1127-1134.

Williams, L.E., Bland, J.H., and Lipson, R.L., (1966):

Cervical spine subluxations and massive osteolysis in The upper extremities in rheumatoid arthritis. Arhtritis and Rheumatism 9:348.

Williams, J.A., Bayliss, E.M., and Shipley, M.E., (1982):

Adouble-blind placebo controlled trial of methylpredn-isolone in active rheumatoid disease. lancet. 2:237-240.

Williams, R.A., Samson, D., Tikerpae, J., Crowne, H., and Gumpel, J.M., (1982):

In vitro studies of ineffective erythropoiesis in R.A.. Ann. Rheum. Dis.. 41:502.

Williams, H.J., Ward, J.R., Reading, J.C., and Eggar, M.J., (1983):

Low dose D-penicillamine Therapy in rheumatoid arthritis. a controlled. double blind clinical Trial. Arth x Rheum.. 26:581-592.

Willkens, R.F., (1985):

Immunomodulating Agents from "Rheumatic Therapeutics" edited by Roth. S.H.. Calabro. J.J.. Paulus, H.E.. and Willkens. R.F.. McGraw-Hill book company, NewYork. 19:324-339.

Wiseman, M.J., (1981):

Dislocation of The manubriosternal joint in rheumatoid arthritis. Annals of The rheumatic Diseases. 40:307-308.

Wolman, L., Darke, C.S., and Young, A., (1965).

The larynx in rheumatoid arthritis. Journal of Laryngology 79:403.

Wright, V., and Hopkins, R., (1976):

Administration of anti-rheumatic drugs. Annals of The Rheumatic Diseases. 35:174-180.

Yates, D.b., and Scott, J.T., (1975):
Rheumatoid synovitis and joint disease. relationship between arthrosocpic and histological changes. Ann. Rtheum. Dis., 34:1.

Yetes, D.B, (1978):
arhtroscopy. arthrography. and synovial biopsy. In "copeman's Textebook of the Rheumatic Diseases" edited by Scott. J.T.. 5th edition. livingstone. London. New vork. P:1022.

Zacharski, L.R., and Kyle, R.A., (1967):
Significance of extensive evaluation of ESR. JAMA. 202:264.

Zilko, P.J., Feeney, D., christiansen, F.T., Hawkins, B.R., and Dawkin, r.L.(1980:
HLA and GM Typing in families with rheumatoid arthritis. arthritis and Rheumatism. 23:767 (Abstract)

Zvaifler, N.J., (1979):
rheumatoid synovitis. an extravascular immune complex disease. Arh x Rheum. 17:297.

Zvaifler, N.J., (1979):
Etiology and pathogenesis of rheumatoid arthritis from Arthritis and allied conditions by Danil. McCarty, Lea Febiger. philadelphia 28:417-428.

بسم الله الرحمن الرحيم

الملخـــــص العربـــي

الغرض من البحث :

دراسة تأثير عقار الدابسون في علاج مرضي الروماتويد المفصلي

طرق مواد البحث :

- أجري البحث علي ٤٢ مريضا بمرض الروماتويد المفصلي وكانت أعمارهم تتراوح بين (٢٢ الي ٦٠ سنة) وكان عددج الإناث ٣٧ مريضة بينما عدد الذكور ٦ مرضي . وقد تم تشخيص حالتهم طبقا للمعايير التي أقرتها الجمعية الأمريكية للروماتيزم . وقد تم إختيارهم من المترددين علي مستشفيات بنها الجامعية .

- ولقد منع المرضي من تعاطي أدوية الروماتويد مثل عقارالذهب والبنسلين لمدة ٢ شهور قبل البدء في إعطاء الدابسون وسمح لهم فقط بأخذ المسكنات والأدوية المضادة للإلتهابات .

طرق البحث:

ا) تاريخ المرض كاملا مع التركيز علي مدة التيبس المفصلي في الصباح .

ب) الفحص الاكلينيكي الشامل مع التركيز علي الجهاز الحركي .

- حصر عدد المفاصل الملتهبة أو التي يحدث عنها ألم إذا حركت في مجال الحركة القصوي لها .

- حصر عدد المفاصل المنتفخة .

- تعيين معامل ريتش لقياس ألم المفاصل الناتج بالضغط لكل الحالات .

- قياس قوة قبضة اليد .

- قياس محيط المفاصل القريبة من المركز بين سلاميات أصابع اليد

ج) الفحص المعملي .

- نسبة الهيموجلوبين في الدم .

- عد كلي ونوعي لكرات الدم البيضاء .

- سرعة ترسيب كرات الدم الحمراء .

- البروتين المتفاعل©

- إختبار لاتكس لمعامل الروماتويد

- وظائف الكبد

- نسبة الكرياتينين في المصل
- نسبة البوليا في الدم

□ وقد اعطي المرض العلاج عشوائيا في مجموعتين .

المجموعة الأولي :(٢٢ مريض) وعولجت بعقار الدابسون .

المجموعة الثانية :(٢١ مريض) وعولجت بالعقار المشابه في الشكل فقط ولكن ليس له تاثير علي المرض وقد اعطي الدابسون بجرعة ٥٠مجم يوميا لمدة اسبوع ثم ١٠٠ مجم يوميا بعد ذلك وتم متابعة المرضي لمدة ٦ شهور .

وقد تم استبعاد ٢ مريض من مجموعة الدابسون . أحدهما بسبب الآثار الجانبية والثاني بسبب عدم الإستفادة من العلاج . كما تم استبعاد مريض واحد من المجموعة الاخري وذلك لعدم الاستفادة

نتائج البحث :

أ) النتائج الأكلينيكية :

١- النقص في مدة التيبس المفصلي في الصباح بالنسبة للمجموعة التي عولجت بعقار الدابسون له قيمة إحصائية عالية وذلك بالمقارنة بالمجموعة التى عولجت بالعقار المشابه .

٢- عقار الدابسون له قيمة إحصائية عالية في تقليل عدد المفاصل الملتهبة والمنتفخة وفي تحسين معامل ريتش لقياس الم المفاصل الناتج بالضغط وذلك بالمقارنة بالعقار المشابه .

٣- عقار الدابسون ليس له قيمة احصائية في تحسن قوة قبضة اليد وذلك بالمقارنة بالعقار المشابه .

٤- عقار الدابسون له قيمة احصائية في نقص محيط المفاصل القريبة من المركز بين سلاميات أصابع اليد وذلك بالمقارنة بالعقار المشابة .

ب) نتائج الفحوص المعملية :

١- انخفاض نسبة الهيموجلوبين بعد العلاج بعقار الدابسون له قيمة احصائية وذلك بالمقارنة بالعقار المشابه .

٢- عقار الدابسون ليس له قيمة احصائية في التاثير علي عدد كرات الدم البيضاء "كلي ونوعي" وذلك بالمقارنة بالعقار المشابه .

٣- انخفاض سرعة ترسيب كرات الدم الحمراء والبروتين المتفاعل "c" بعد العلاج بعقار الدابسون له قيمة احصائية عالية وذلك بالمقارنة بالعقار المشابه .

٤- اما بالنسبة لمعامل الروماتويد فلا يوجد تغيير له قيمة احصائية في المجموعة التي عولجت بعقار الدابسون وذلك بالمقارنة بالمجموعة التي عولجت بالعقار المشابه .

٥- لوحظ ان بعض الفحوصات المعملية بالنسبة لوظائف الكبد ونسبة الكريانتين في المصل

والبولينا في الدم لم تظهر تغييرات ذات قيمة احصائية بعد العلاج بعقار الدابسون وذلك بالمقارنة بالعلاج المشابه .

□ تبين من التقييم النهائي للتحسين في الحالات تبعا للدلالات الاكلينيكية والمعملية معا ان لعقار الدابسون تاثير في النشاط الروماتيزمي لمرضي الروماتويد المفصلي

-علي الرغم من التحسن الملموس الذي أظهره عقار الدابسون في علاج الروماتويد المفصلي في هذه الدراسة إلا اننا نحتاج لمتابعة طويلة ودراسات اخري لتقييم القيمة الحقيقية ودوره في علاج هذا المرض المزمن

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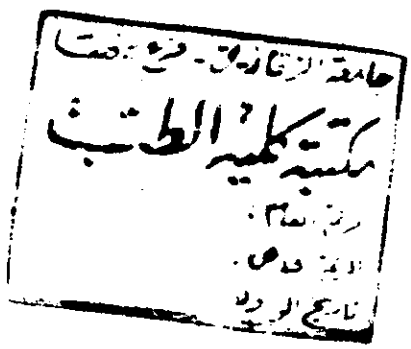

جامعة الزقازيق
كلية طب بنها
قسم الروماتيزم والتأهيل

إستعمال عقار الدابسون في علاج مرضى الروماتويد المفصلي

رسالة مقدمة من

الطبيب / سامي السعيد محمد أحمد عجيلة

للحصول على درجة

الدكتوراه في الروماتيزم والتأهيل

١٩٩٢