

Rheumatoid Arthritis: A Historical and Biopsychosocial Perspective

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1. Introduction

Rheumatoid arthritis (RA) is a relatively common, disabling, autoimmune disease that is characterized by progressive joint disorder, significant pain and functional disability. Its prevalence is estimated at 0.5 - 1.0 percent of adults worldwide (Kvein, 2004), and the disease continues to cause significant morbidity and premature mortality.

Symmetric highly inflammatory polyarthritis of peripheral joints is the hallmark of the disease. The condition is also systemic in that it often affects many extra-articular tissues throughout the body, including skin, blood vessels, heart, lungs, and muscles. The gradual involvement of multiple joints into pathophysiological process eventually results in articular destruction, ensuing instability, deformity and collateral pain. As the pathology progresses, chronic pain and functional disability dominates one's life and lessens everyday enjoyment and comforts.

Physical in nature, the disease also exacts an emotional toll that often leads to unfortunate psychiatric sequelae. It is not at all surprising that in addition to joint deformity, disability, dolour, and excess mortality, on average one in five patients with rheumatoid arthritis will experience depression.

Many new insights into epidemiology, pathogenesis, outcomes measurement, and pharmacologic treatment of rheumatoid arthritis have occurred in recent years. Applications of historical analyses to the development of a cogent etiologic theory of rheumatoid arthritis have been limited to date (Entezami et al, 2011). In this chapter, the author presents the major points of evidence and conclusions that have been drawn from historical, clinical and research material in the study of rheumatic diseases.

2. Historical conceptualisation

2.1 Nosology in evolution

Although the appearance of rheumatoid arthritis was noted in radiological examination of skeletal remains of Tennessee Indians from as early as 4500 BC, we do not find documented evidence until much later. It is said that realisation of how "taxing" arthritis can be, made Roman Emperor Diocletian free his citizens with the disorder from paying taxes. The term '*rheumatism*' dates back to 1630, and is derived from the Greek '*rheumatōs*' that means 'flowing'. It signified an evil humour or mucus that was thought to flow from the brain to the joints, causing inflammation, pain and deformities. Short (Short, 1974)

traced the first adequate description of what was probably rheumatoid arthritis to Thomas Sydenham (1624-1689) and emphasised that medical literature before Sydenham's time may have confused gout and other forms of polyarthritis as manifestations of the same disease.

Analysis of the hands in the Flemish paintings and works attributed to Peter Paul Rubens seems to show hand lesions resembling those of rheumatoid arthritis. To illustrate this, on the reproduction here, swelling of three metacarpophalangeal joints are clearly visible on the right hand of Erasmus of Rotterdam painted by the Flemish Quinten Metsys in 1529, (FIG.1). Desiderius Erasmus (1467-1536), the Dutch renaissance scholar is often quoted for his famous aphorism "prevention is better than cure" and is recognised as the Prince of Humanists for his progressive writings of the time. This painting is testimony to the high cultural climate of the time, and evidence of the links between two great humanist thinkers, Erasmus of Rotterdam and Sir Thomas More, both of whom contributed to the publication of Utopia.



Fig. 1. **Quinten Metsys, Portrait of Erasmus of Rotterdam, 1517.** Oil on panel, 59 x 46.5 cm. Reproduced with permission from National Gallery of Antique Art, Rome.

While none of the deformities or swellings is indisputable examples of rheumatoid arthritis, they do at least suggest that the painters must have been confronted with rheumatoid-like lesions in their models. It is established that Rubens was well qualified to accurately depict arthritic deformities, as he had a personal familiarity with arthritis. Although history is uncertain as to who suffered from the disease, Rubens or his long-term co-author, it is easy to imagine artists' working surroundings at the time: ancient damp art studios, oils, powders and drying canvases everywhere – a portrayal of an "ideal" environment for triggering a rheumatic flare-up and causing inflammation.

These observations suggest that rheumatoid arthritis is not a modern disease and was present several centuries before its description as a separate entity by Augustine-Jacob Landré Beauvais' in 1800 (Dequeker J. 1977; Appelboom T. et al, 1981; Dequeker J, Rico H. 1992). A generation later, in 1859, Sir Alfred Garrod, a physician from Ipswich who later was appointed Professor of Materia Medica and Therapeutics and of Medicine, coined the name 'rheumatoid arthritis'. In his renowned treatise with illustrations (Garrod, 1859), he considered the main differential diagnosis, including rheumatic gout of Fuller, chronic rheumatism of Heberden, scorbutic rheumatism and rheumalgia, and rejected them all in favour of 'rheumatoid arthritis' the name he chose for the disease. He divided it into two types: generalised and localised and identified three forms: acute, chronic and irregular. The name has remained ever since.

2.2 Diagnostically diverse group of disorders

Rheumatoid arthritis belongs to a diverse group of musculoskeletal disorders ("arthritis"): there are more than 200 types of these diseases that also encompass osteoarthritis, Still's disease, ankylosing spondylitis, and Reiter's syndrome. Some sources also name Felty's syndrome and Sjogren's syndrome as related disorders (Wilson et al, 1991). Some of these are very serious diseases that can be difficult to diagnose and treat. For instance, hemochromatosis (build up of iron in the body) was misdiagnosed as rheumatoid arthritis in the past (Espinosa-Morales et al, 1998).

Skeletal evidence of primary ankle (kaki) **osteoarthritis** has been discovered in dinosaurs! In 1715 William Musgrave published the second edition of his most important medical work '*De arthritide symptomatica*' which concerned arthritis and its effects (Cameron, 2004). A common feature in all osteoarthritis is a loss of cartilage in association with bone features such as osteophytes and subchondral bone sclerosis. Large epidemiologic studies of osteoarthritis performed over a period of 30 years (Peyron, 1986) have confirmed that osteoarthritis is a ubiquitous condition, that it is linked to age, that it is more frequent and more widespread in women older than 45 years of age, and that the mechanical overuse of the joints is probably instrumental in the occurrence and the location of certain cases of osteoarthritis. Epidemiologic evidence points to the existence of an entity of "generalised osteoarthritis" composed of three or more locations with involvement of the interphalangeals. Heredity, in cases associated with distal interphalangeal osteoarthritis, and inflammation, in cases with proximal interphalangeal osteoarthritis, are the factors found to be most closely correlated to generalised osteoarthritis. Surveys of several series of osteoarthritis of the hip have pointed to the existence of several clinicoradiologic subsets that could have different clinical correlates and various pathophysiological mechanisms. Interestingly, according to a Boston University study (Hunter *et al*, 2004), ever since their invention five thousand years ago, chopsticks have been a source of osteoarthritis. This epidemiologic study investigated the relationship of chopsticks use to hand arthropathy. The results suggest that chopsticks use is associated with an increased prevalence of osteoarthritis in the interphalangeal joint of the thumb, and in the second and third interphalangeal and metacarpophalangeal joints.

In 1897 Sir George Frederick Still published a paper entitled 'On a form of chronic joint disease in children', that was the subject of his MD thesis, where he described several types of juvenile rheumatoid arthritis (FIG.2) and introduced an previously unrecognizable disease, known, as it is today, as **Still's disease** or systemic-onset juvenile rheumatoid

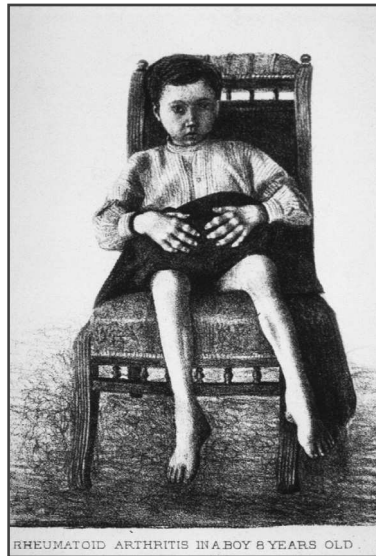


Fig. 2. Rheumatoid arthritis in an 8 yr old boy. From a slide collection of images from Still's 'On a form of chronic joint disease in children' reproduced with permission from Professor Patricia Woo.

arthritis. He defined the condition as a 'chronic progressive enlargement of joints, associated with general enlargement of glands and enlargement of spleen' with the onset 'almost always before the second dentition' (Still, 1897). Still concluded that this condition differed from rheumatoid arthritis in adults in the enlargement of glands and spleen and in the absence of bony change.

Since then adult onset Still's disease (AOSD) has been described as an acute febrile illness in young adults. It usually affects multiple organs, but is a diagnosis of exclusion. The aetiology of AOSD is unknown; however, a number of infectious triggers have been suggested, including viruses and bacterial pathogens including *Mycoplasma pneumoniae*. Clinical features include a high fever, arthralgia and arthritis, pharyngitis, typical rash (evanescent salmon-coloured, macular or maculopapular eruption), lymphadenopathy, and serositis. Chronic arthritis and constitutional symptoms are common. The triad of fever, rash, and arthralgia are often absent during the first month of the illness. A quotidian (daily, spiking) or "double-quotidian" fever curve is a hallmark of the disease. The usual joints affected are wrists, knees, and ankles in descending order. Several diagnostic criteria sets for AOSD have been proposed. Two of these sets of criteria are shown in the TABLE 1.1. 1987 and 1992 Criteria for the Classification of Adult Onset of Still's Disease.

It is interesting that a recent case series identified patients with **ankylosing spondylitis** who also meet the criteria of adult onset Still's disease (Akkoc et al, 2008). The ankylosing spondylitis existed since ancient times, as verified by the skeletal remains of a 5000-year-old Egyptian mummy with evidence of 'bamboo spine' (Calin, 1985). It is a chronic, painful, degenerative, inflammatory arthritis primarily affecting the spine and sacroiliac joints; the ossification of joints and entheses primarily of the axial skeleton are known as 'bamboo spine'. It was recognised as distinct from arthritis by Galen as early as the second century

| Diagnostic Criteria I | Diagnostic Criteria II |
|---|---|
| <p>Requires ALL of the following:</p> <ul style="list-style-type: none"> • Fever > 39 degrees • Arthralgia or arthritis • Rheumatoid factor < 1:80 • ANA < 1:100 <p>In addition to ANY TWO of the following:</p> <ul style="list-style-type: none"> • WBC count > 15,000 • Stills rash • Pleuritis or Pericarditis • Hepatomegaly, Splenomegaly, or Lymphadenopathy | <p>Presence of 5 or more criteria, of which at least 2 are Major - yields 96% sensitivity; 92% specificity</p> <p>Major Criteria</p> <ul style="list-style-type: none"> • Fever > 39 degrees > 1 week • Arthralgia/arthritis > 2 weeks • Typical rash • WBC > 10 K with 80% PMN's <p>Minor Criteria</p> <ul style="list-style-type: none"> • Sore throat • Lymphadenopathy • Increased LFT's • RF and ANA negative |
| <p>According to: Cush JJ, Medsger TA, Jr, Christy WC, et al. Adult-onset Still's disease: Clinical course and outcome. <i>Arthritis Rheum</i> 30:186, 1987.</p> | <p>According to: Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. <i>J Rheumatol</i> 19:424, 1992.</p> |

Table 1.1 Diagnostic Criteria

(Dieppe, 1988), and the anatomist and surgeon Realdo Colombo characterised the condition in 1559 (Benoist, 1995). However, it was not until 1892, when Russian neurologist Vladimir Michailovich Bekhterev published a series of papers, that the syndrome was fully described (Bechterev, 1892). Later, Adolf Strümpel of Germany (1897) and Pierre Marie of France (1898) also gave adequate descriptions which permitted an accurate diagnosis of ankylosing spondylitis prior to severe spinal deformity. For this reason, ankylosing spondylitis is also known as Bekhterev's Disease or Marie-Strümpel Disease. Bekhterev advocated physiotherapy and the benefits of hypnosis for the patients with rheumatic spondylitis, the latter treatment method he studied under the direction of Professor Jean-Martin Charcot in Salpetriere (Kannabikh, 1925).

Reiter's syndrome was named after Hans Reiter (Reiter, 1916), who reported a case of a soldier with the triad of urethritis, arthritis and conjunctivitis, following an episode of bloody diarrhea. However, the history of this constellation of signs actually predates his description. Urethritis, arthritis and conjunctivitis have subsequently remained as the essential components of this syndrome, but some feel that the eye involvement is so often minimal or insignificant that it need not necessarily be present to make the diagnosis (Gaston & Lillicrap, 2003). Although Reiter's syndrome and psoriatic arthritis are ordinarily two rather discrete entities, there is a significant zone of diagnostic overlap in patients with cutaneous lesions. Both diseases may coexist in the same patient, or Reiter's syndrome seemingly may evolve into psoriatic arthritis. Reiter's syndrome in recent medical literature is simply referred to as reactive arthritis which may or may not be accompanied by extraintestinal manifestations. Salmonella has been the most frequently studied bacteria associated with reactive arthritis. Overall, studies have found rates of Salmonella-associated reactive arthritis to vary between 6 and 30% (Hill Gaston, & Lillicrap, 2003). The term Reiter's syndrome has fallen into disfavour, owing to its author's reputation as a high-

ranking Nazi official who was responsible for medical experiments in concentration camps (Panush, et al., 2003; Petersel & Sigal, 2005).

Felty's syndrome is an uncommon extra-articular manifestation of rheumatoid arthritis. First described in 1924, Felty syndrome is a potentially serious condition that is associated with seropositive rheumatoid arthritis. Felty syndrome is characterized by the triad of rheumatoid arthritis, splenomegaly, and granulocytopenia. Although many patients are asymptomatic, some develop serious and life-threatening infections secondary to granulocytopenia. It is more prevalent among women around 60 with a long history of severe articular disease, positive rheumatoid factor, and who carry the HLA-DR4 allele (Ghavami *et al*, 2005).

In 1933, Swedish physician Henrik Sjögren observed a large number of his female patients were experiencing dry eyes and mouths along with their arthritis symptoms. The condition became known as **Sjögren's syndrome**. Primary Sjögren's syndrome is defined when only the ocular (keratoconjunctivitis sicca) and oral (xerostomia) components are present, while the secondary form refers to the association with a connective tissue disorder, especially rheumatoid arthritis, or other illness such as AIDS, hepatitis C infection, or biliary cirrhosis. In recent years, Sjögren's syndrome has also been reported to be associated with chronic graft-versus-host disease after allogeneic bone marrow transplantation. Sjögren's syndrome is a common, but often overlooked disorder. Patients with severe disease run a forty-times risk of developing lymphoma usually of the B cell type (Parke and Buchanan, 1998).

2.1.3 Formation of rheumatology as a speciality

The important work of the time by Boyle, Richardson and Doll on 'The Scientific Method' (Boyle, 1954; Doll, 1954) illustrate the beginning of a change in the practice of physical medicine in UK. The evolution of rheumatology as a subspecialty of General Medicine in England since the 1960s was happening alongside the progressive developments in clinical science, and in academic provision across the country. This initiative aimed at separating the often overlapping and competing communities of physical medicine, rehabilitation, rheumatology and internal medicine.

TJ (Lord) Horder, a distinguished London physician and (Sir) Stanley Davidson, who served as a member of the Empire Rheumatism Council re-branded clinical rheumatology on a scientific basis alongside the evolving research disciplines in pathology and clinical pharmacology. The Empire Rheumatism Council, later known as the Arthritis and Rheumatism Council, also changed its emphasis from welfare to the promotion of scientific research and medical education, while developing charities focused on the welfare of patients with rheumatic disorders instead.

The link with General Medicine, the dissolution of the link with Physical Medicine and Rehabilitation, the growth of clinical science and the increasing sophistication of therapeutics have all influenced the change in paradigm. For example, it was not until 1953 that 'Rheumatoid Arthritis' was in the title of any article in UK and not until 1958 did a systemic rheumatic disease feature at all. As regards therapeutics, salicylates, corticosteroids and the early NSAIDs featured intermittently in clinical reports. Clinical trials were rare in the 1950s, but large clinical series were commonly reported, such as 1723 cases of meniscectomy (Wynn et al, 1958).

2.2 Aetiological debate

Despite the notable advances in knowledge regarding progression of rheumatoid arthritis, its cause remains elusive. In fact, there probably is not an exact cause for it. Researchers now

are debating whether rheumatoid arthritis is one disease or several different diseases with common features. It appears to be a multi-factorial disease in which there are important genetic and environmental influences. There are no reports of clustering in space or time that would support an infectious cause. Jobanputra (Jobanputra et al, 1995) studied and suspected such infectious agents, as mycobacteria, Epstein-Barr virus and parvovirus as causal agents, but without any conclusive or convincing evidence. Sex hormones are implicated since there is an increased incidence in women and RA mostly improves in pregnancy, and relapses post-partum. Nulliparous women, women in the post-partum period, and women who have an early menarche have a greater risk of developing RA (Silman, 1998). While environmental stressors are likely to be involved, no definite environmental factors that precipitate disease onset have been identified. Current research is focused on elucidating the complex interactions of genetic, environmental, hormonal and auto-immune pathways. It becomes more evident that these factors nourish the immunopathogenesis on the initial stages of this disease and continue to fuel its maintenance and progression.

2.2.1 Stress theories

One of the oldest of explanation was the stress hormone hypothesis championed by Hans Selye (Selye 1949 & 1950). Roughly, his contention was that hormones released by the body, especially those released by the jacket of the adrenal glands, cause an adverse reaction to the joint tissues when they are released in excessive amounts, or in the wrong ratios under the conditions of environmental or psychological stress. His concept was generalised and only mentioned rheumatoid arthritis as an unlikely possibility. The theory had some plausibility since arthritis can be produced by injecting deoxycorticosterone, which is a potassium excreting hormone, into a patient with Addison's disease or reproduced in similar animal studies (Selye, 1944). The dramatic effect that cortisone has on arthritis was demonstrated first in 1948 by Edward C. Kendall and Philip S. Hench at the Mayo Clinic in Rochester, Minnesota. Their discovery stemmed from the astute clinical observation that a woman with severe RA felt much better during pregnancy. They found what was responsible. It was a hormone from the outer part (the cortex) of the adrenal glands that they called 'cortisone'. On September 21, 1948, Hench gave a synthesised version of cortisone developed by Kendall to a patient with arthritis and it became the first 'miracle drug' due to its powerful anti-inflammatory and other effects. In 1950 they shared the Nobel Prize in physiology for their discoveries relating to the hormones of the adrenal cortex. The question of whether patients with rheumatoid arthritis might have a defective hypothalamo-pituitary-adrenal axis was first raised then. It was initially hypothesised that this was due to an impaired ability of RA patients to synthesise sufficient amounts of endogenous glucocorticoids, but intensive investigations over the next few decades failed to reveal any significant defects in HPA axis activity in RA patients. The literature review provided no compelling evidence for significant differences in either basal or stress-stimulated HPA axis activity in RA patients compared with healthy individuals. However, Jessop and Harbuz (1999) did highlight an inherent defect, which resided in the inability of RA patients to mount an appropriately enhanced glucocorticoid response to increased secretion of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) - α . 'In other words', they concluded, 'the HPA axis response in RA is defective precisely because it is normal'. Following an insulin-induced hypoglycaemia, which tests the HPA axis at all levels, there were no observed differences in serum cortisol responses between patients with active RA

and patients in remission (Demir et al, 1999). This study did not include non-RA subjects as controls, and there was no ACTH response to hypoglycaemia in either test group, suggesting a possible methodological problem. Although the HPA axis in RA is defective because its activity is not increased in response to inflammatory cytokines, as might be predicted from observations of increased corticosterone in rodent models of inflammation (Harbuz, 2002), the current evidence suggest that the HPA axis is not materially different in RA compared with normal healthy subjects under most experimental conditions (Jessop, Harbuz, 2005). Stress theories did not always emphasize steroid hormones. Histamine was suggested as possibly being involved by two University of Utah scientists, Chemist Henry Eyring and Anatomist Thomas F. Dougherty in 1955 (Eyring and Dougherty, 1955). Their theory stated that stress sets off a destructive chain reaction among the body cells with histamine acting as a destructive agent. Each cell is in a membrane envelope and, as long as the membrane is relatively impermeable, the cell functions normally. Under stress, however, the membrane starts to deteriorate. Histamine, which is normally present inside the cell when the cell is healthy, is violently released and stimulated by the cell breakdown. It attacks the disintegrating cell, which swells and bursts, liberating still more histamine to attack neighbouring cells. Over long periods of stress, the spreading destruction can lead to serious illness and may be present in every fatal illness, including cancer.

Supporting evidence of histamine hyperproduction comes from the study by Permin and colleagues (Permin et al, 1981). They found that basophilocytes from patients with rheumatoid arthritis responded to leukocyte nuclei from normal persons with histamine release and recorded 3.5 times as much histamine production in arthritics after the challenge than normally expected. A role of histamine in RA is also supported by the findings from the same study of clinical improvement during treatment with H1 and H2 antihistamines in six of 12 patients with RA in active phase, whereas four showed definite deterioration.

2.2.2 Autoimmune hypothesis

The most popular current hypothesis is the autoimmune hypothesis. Many do not even regard this concept as a hypothesis, but as a proven theory, as investigations into the autoimmune hypothesis are well funded. When rheumatoid arthritis presents, the immune system overcompensates and acts, attacking the joints and the body in general. The same thing occurs with other autoimmune diseases; the immunological mechanisms that manifest in these diseases have been identified, but there is still no explanation as to why this occurs.

Immunopathogenesis of RA is multifactorial. Evidence suggests that an interaction between an unknown exogenous or endogenous antigen via antigen presenting cells and CD4 T helper cells are involved in the induction of the immune response in RA. Subsequent recruitment and activation of monocytes and macrophages occurs with the secretion of pro-inflammatory cytokines, in particular TNF- α and IL-1 into the synovial cavity. The release of these cytokines mediates tissue destruction by activation of chondrocytes and fibroblasts which release collagenases and metalloproteinases with resultant cartilage loss and bone erosion. B lymphocyte dysregulation, resulting in the production of rheumatoid factor and other auto-antibodies, as well as in the formation of immune complexes and the release of destructive mediators, also contribute to this process. Rheumatoid factor, an autoimmune response to IgG is a key feature of RA. High levels are relatively specific for RA but rheumatoid factor may also occur in other chronic diseases and is absent in around 30% of patients with established RA. Other auto-antigens have been proposed but as yet no single antigen has been incriminated (Jobanputra, 1992). Ankylosing spondylitis and rheumatoid

arthritis share many common features. However the presence of rheumatoid factor, histologically classic rheumatoid nodules, and the histocompatibility cell wall antigen (HLA-B27) helps distinguish one from the other. A much higher association of antigen HLA-B27, which is a known immune factor with the disorders in the arthritic group, such as Reiter's syndrome and ankylosing spondylitis (López-Larrea et al, 1998), has tended to reinforce evidence for autoimmune aetiology of RA.

The hypothesis that rheumatoid arthritis is an allergy is in the same general category as the autoimmune hypothesis. Such a hypothesis has the advantage, not shared by the autoimmune hypothesis directly, of advancing an environmental factor, which is almost certainly involved. The wide geographical variations virtually ensure this. There is evidence from several well documented case reports (Buchanan et al, 1991) that occasional patients with rheumatoid arthritis may develop an aggravation of their arthritis, as a result of allergy to some ingredient in their diet. A variety of foodstuffs have been implicated including milk and milk products, corn and cereals. Total fasting results in an improvement in rheumatoid arthritis, but appears to be mediated by diminution in production of chemical mediators of inflammation, rather than by elimination of a dietary allergen. According to Buchanan (Buchanan et al, 1991), there is conflicting evidence from the studies that used various intestinal probes, that patients with rheumatoid arthritis may have a 'leaky' intestinal mucosa, allowing the food allergens to be more easily absorbed. Clinical therapeutic trials of exclusion diets have employed the standard strategy of the double-blind randomised method. However, this presupposes that patients entered into such a study are capable of improvement with dietary manipulation. Since this is often not the case, a more appropriate method would be to employ the 'intensive research design', also known as 'single case experiment' and 'N of 1' study. The hypothesis pointing towards 'masked food intolerance' is an attractive theory, but one that is extremely difficult to prove in practice.

2.2.3 Genetic basis of Rheumatoid Arthritis

Support for a genetic predisposition for rheumatoid arthritis has come from the studies reporting rheumatoid arthritis clusters in families. Formal genetic studies have confirmed this familial aggregation and genetic influence is estimated at 50 to 60% (Ollier et al, 1999). Studies in monozygotic twins have shown a concordance rate of 15% - 30% and a relative risk of 3.5 for rheumatoid arthritis developing in monozygotic versus dizygotic twins of affected cases. A high prevalence rate of 5% - 6% has been described in some Native American populations, suggesting a higher genetic burden of rheumatoid arthritis risk genes. Differences in the prevalence rates in other ethnic groups are rather small and are partially explained by differences in disease ascertainment.

Interactive genetic effects are suspected to modulate the impact of individual disease-risk genes and are likely to contribute to the low penetrance. Genetic risk factors not only determine susceptibility for the disease but also correlate with the disease severity and phenotype, providing the unique opportunity to use genetic markers as prognostic tools in the management of rheumatoid arthritis. A measure used to estimate the genetic component to the disease is the coefficient of familial clustering, λ_s , defined as the ratio of the prevalence in affected siblings to the population prevalence. For rheumatoid arthritis, λ_s ranges from 2 to 12 in first-degree relatives of patients, depending on the published data (Dieudé & Cornélis, 2005). Although clearly supporting the influence of the genetic factors, this λ_s is rather low compared with other autoimmune diseases or common genetic diseases, leaving considerable room for any environmental or stochastic events in the pathogenesis of

the disease. In part, λ s may be rather low because rheumatoid arthritis is a heterogeneous syndrome that includes several genetically semi-homogeneous subsets.

The genetic system studied most thoroughly is the major histocompatibility complex (MHC). In the initial studies, rheumatoid arthritis was shown to be associated with human leukocyte antigen (HLA)-DR4 (Stastny et al, 1978). The association studies in different ethnic populations support the concept that HLA-DRB1 alleles, expressing a particular sequence motif are over-represented among people with rheumatoid arthritis (Ollier et al, 1999). This sequence polymorphism is characterized by a glutamine or arginine at position 70, a lysine or alanine at position 71, and an alanine at position 74. Alleles with a negatively charged amino acid at any one of these positions are not associated with the disease. MHC genes are not the only germline-encoded genes influencing susceptibility to rheumatoid arthritis. Female sex clearly increases the risk, and female patients develop a different phenotype of the disease than do male patients. However, no sex-linked genes have been identified as disease-risk genes. Several consortiums have started genome-wide searches, using affected sibling pairs (Seldin et al, 1999). Eventually, the candidate gene approach may be more sensitive for identifying risk genes, in particular when considering the heterogeneity of the disease severity and phenotype. The recent definition of single nucleotide polymorphisms throughout the human genome has increased significantly the feasibility of this approach. Studies of T-cell receptor (TCR) and immunoglobulin genes have not been revealing; several cytokine polymorphisms, including tumour necrosis factor (TNF)- α and interferon (IFN)- γ were described to influence disease severity, but studies are needed to confirm this hypothesis.

2.3 Diagnostic considerations

Reliable measurement is often a prerequisite of effective intervention, or at least of enabling clinical trials. Rheumatoid arthritis is diagnosed from a constellation of clinical and laboratory or radiographic abnormalities. Diagnosis may be obvious in some but in others it may be more difficult and require a period of clinical observation. Classification criteria for RA have been devised. The 1987 revised criteria for the classification of rheumatoid arthritis (Arnett et al, 1988) are shown in TABLE 1.4; it superseded The American Rheumatism Association criteria of 1958. These criteria were derived from a group of typical patients who had been diagnosed with RA and had well-established disease. They have limited utility in routine practice and most clinicians diagnose RA without formal reference to such criteria, and many patients do not meet formal criteria at least early in disease (Harrison et al, 1998). Criteria 1 through 4 must have been present for at least 6 weeks. Rheumatoid arthritis is defined by the presence of 4 or more criteria, and no further qualifications (classic, definite, or probable) or list of exclusions are required. In addition, a "classification tree" schema is presented which performs equally as well as the traditional (4 of 7) format. The newer criteria demonstrated 91-94% sensitivity and 89% specificity for RA when compared with non-RA rheumatic disease control subjects. Criteria were also developed as an algorithm and these are more readily met in clinical practice (Emery et al, 1997).

Two diagnostic tests are included in the criteria: rheumatoid factor and X-ray changes. Rheumatoid factor (RF), measured in routine blood samples, is a circulating IgM autoantibody that is directed against IgG molecules. In established disease, IgM- RF can be detected with a sensitivity of 60-70% and a specificity of 80-90% (Van Gaalen et al, 2004). Another antibody against the cyclic citrulline protein (CCP) specific for RA was discovered later. In a meta-analysis published in 2007 it was found that anti-CCP antibody displays

sensitivities comparable to that of RF (approximately 80%) but with superior specificity (98%) (Nishimura et al, 2007). Early in disease radiographs may show soft tissue swelling and reduced bone density around affected joints. Later there may be evidence of joint damage such as joint erosions (focal loss of bone and cartilage often near the joint margin) or a reduced joint space (indicating diffuse cartilage loss). With continued joint damage there may be extensive joint destruction, features of joint deformity or instability, and bony ankylosis. With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. At an earlier stage surgical treatment such as removal of synovial tissues (synovectomy) or other soft tissue procedures such as tendon release or repair may also be necessary.

| Criterion | Definition |
|---------------------------------------|---|
| 1. Morning stiffness | Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement |
| 2. Arthritis of 3 or more joint areas | At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints |
| 3. Arthritis of hand joints | At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint |
| 4. Symmetric arthritis | Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry) |
| 5. Rheumatoid nodules | Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician |
| 6. Serum rheumatoid factor | Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects |
| 7. Radiographic changes | Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) |

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.

Table 1.4 1987 Criteria for the Classification of Acute Arthritis of RA

Among additional diagnostic tests are acute-phase reactants – the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level that correlate with the degree of synovial inflammation. They are useful for following the course of inflammatory activity in an individual patient. Other abnormalities include hypergammaglobulinemia, thrombocytosis, and eosinophilia. These occur more often in patients with severe disease, high RF titer, rheumatoid nodules, and extra-articular manifestations.

2.4 Trends in pharmacological and biological therapy

In more recent years, a number of new exciting therapeutic options have become available, especially with the development of the biologic drugs, thus causing evolution of rheumatological science to spiral. This trend reflects the application of knowledge obtained from advancements in understanding of disease pathogenesis and underlying molecular mechanisms. This therapeutic philosophy has drawn on the model of oncology, with early diagnosis and aggressive treatment. While this has been in parallel with and to an extent dependent upon, sophisticated new imaging techniques such as MRI, clinicians have thought along these lines for many years (Emery, Gough, 1991). A number of these therapies are outlined below, including the various biological modifiers, in particular, anti-tumour necrosis factor- α agents and interleukin-1 (IL-1) receptor antagonists, which have been developed in recognition of the role of pro-inflammatory cytokines in RA. Also notable, is the current interest centering on the development and trials with B cell depletion therapies, specifically rituximab, in patients with RA. This demonstrates acknowledgment for a more significant role for B cells in the aetiology of RA, in contrast to the long held view that RA was a predominantly T cell mediated disease. The main categories of medications used to treat RA considered below.

2.4.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

It has been shown that NSAIDs cause quite distinct and severe biochemical damage during drug absorption (uncoupling of mitochondrial oxidative phosphorylation proving to be most important) which results in increased intestinal permeability. All commonly used NSAIDs, apart from aspirin and nabumetone, are associated with increased intestinal permeability in man. Whilst reversible in the short term, it may take months to improve following prolonged NSAID use (Bjarnason et al, 1993). Avoiding NSAIDs is advisable in patients with inflammatory bowel disease (Kane et al, 2001).

2.4.2 Disease Modifying Antirheumatic Drugs (DMARDs)

DMARDs are used with NSAIDs and/or prednisone to slow joint destruction caused by RA over time. Examples of these drugs are methotrexate, injectable and oral gold, penicillamine, azathioprine, chloroquine, hydroxychloroquine, and sulfasalazine. DMARDs, particularly methotrexate, have been the standard for aggressively treating RA. Recently, studies have shown that the most aggressive treatment for controlling RA may be the combination of methotrexate and another drug, particularly biologic response modifiers (Olsen, 2006). The dual drug treatment seems to create a more effective treatment, especially for people who may not have success with or who have built up a resistance to, methotrexate or another drug alone. It appears that these combination drug therapies might become the new road to follow in treating RA. Oral corticosteroids, or steroids, are powerful anti-inflammatory drugs that are used to quickly reduce inflammation. These drugs include prednisone and

prednisolone and are most often used in combination with DMARDs, which significantly enhances the benefits of DMARDs.

2.4.3 Biologic response modifiers

“Biologics” directly modify the immune system by inhibiting cytokines or B and T immune cells, which contribute to inflammation. Two types of agents can be used to eliminate circulating TNF: recombinant soluble receptors and monoclonal antibodies to TNF. There are three agents that were originally approved for patients with RA which inhibit the action of TNF- α ; - infliximab, etanercept and adalimumab. Two additional novel TNF antagonists, Certolizumab pegol and Golimumab have recently been indicated for patients with RA for the treatment of moderate to severe, active RA in adult patients when the response to conventional DMARDs including methotrexate, has been inadequate.

Etanercept, a soluble TNF receptor, is labeled for use in monotherapy and combination therapy with methotrexate for arthritis (NICE guidelines, 2002). The TNF- α blocking agent infliximab is labelled for use in combination with methotrexate for the treatment of RA (NICE guidelines, 2002). Adalimumab is a recombinant human IgG1 monoclonal antibody that binds TNF- α , thereby precluding binding to its receptor. Enthusiastic support for early intervention with TNF- α inhibitors for patients with RA comes with a strong safety message. Although infusion reactions and other AEs are infrequent, they may be very serious in some patients, in particular when complications associated with opportunistic infections occur. Certolizumab pegol, which targets TNF- α with a different mechanism of action than widely used biologics, was initially investigated for Crohn's disease but has now been shown to be effective for rheumatoid arthritis. There have been three significant clinical trials demonstrating the efficacy of certolizumab pegol in active rheumatoid arthritis; two with combination methotrexate and one with monotherapy (Ruiz et al, 2011). Significant improvements were observed at 24 weeks and at 52 weeks with the approved dose of 200 mg certolizumab pegol. The most common adverse events with certolizumab pegol 200 mg were: upper respiratory tract infections, hypertension and nasopharyngitis (Ruiz et al, 2011). Golimumab is a humanized inhibitor of Tumor necrosis factor-alpha, recently approved for the treatment of RA. Recent Cochrane systematic review (Singh et al, 2010), identified four Randomised Control Trials with 1,231 patients treated with golimumab and 483 patients treated with placebo. The authors concluded that Golimumab-treated patients were significantly more likely to achieve remission, low disease activity and improvement in functional ability compared to placebo (all statistically significant). No significant differences were noted between golimumab and placebo regarding serious adverse events, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to adverse events and inefficacy and deaths.

2.4.4 Interleukin 1 receptor antagonists

Interleukin 1 is a pro-inflammatory cytokine produced by stimulated monocytes, macrophages and some specialised synovial lining cells. IL-1 receptor antagonist competes with IL-1 for binding to the receptor, subsequently down regulating IL-1 actions. By stimulating the release of matrix metalloproteinases and increasing bone resorption by effects on osteoclasts, IL-1 has been shown to have a significant role in RA pathogenesis, particularly in regards cartilage and bone erosion. Mice deficient of IL-1 receptor antagonist, demonstrate the development of inflammatory arthritis similar to RA (Horai et al, 2000). In

addition, patients with RA have been shown to have lower IL-1 receptor antagonist levels than anticipated for the level of IL-1 in the joint (Arend et al, 1998). It was hypothesized that addressing this imbalance, with a recombinant IL-1 receptor antagonist could be beneficial in RA and anakinra was thus developed for this purpose (Fleischmann et al, 2003). Anakinra is administered by daily subcutaneous injection. The recombinant humanized anti-IL-6 receptor antibody tocilizumab is an innovative drug for the treatment of rheumatoid arthritis. Tocilizumab is generally well tolerated and efficacious in patients refractive to conventional DMARD therapies (Ohsugi, Kishimoto, 2008).

2.4.5 Abatacept

Abatacept selectively modulates the co-stimulatory signal required for full T cell activation. The agent, which binds to CD80 and CD86 on antigen-presenting cells, blocking the engagement of CD28 on T cells and thus preventing T cell activation, acts earlier in the inflammatory cascade than do other biologic therapies by directly inhibiting the activation of T cells and the secondary activation of macrophages and B cells. Abatacept is administered in a 30min infusion. Kremer provided data that originated from his clinical trial (Kremer et al, 2005), demonstrating that the combination of abatacept and methotrexate improves the signs and symptoms, physical functioning, and quality of life of patients with active RA.

2.4.6 B cell depletion therapy

Contrary to the long held view that RA is a predominantly T cell mediated disease, the important role of B cells in disease aetiology is supported by development and trials with B cell depletion therapies notably rituximab. B cells contribute to the pathogenesis of RA via a number of proposed mechanisms including; presentation of antigen complexes with IgG to T cells, and T cell independent generation of TNF- α by tissue macrophages after stimulation by oligomeric IgG rheumatoid factor (RF) immune complexes (Fleischmann et al, 2003). In addition, the ability of IgG RF B cells to self perpetuate due to secretion of own antigen, provided rationale for the proposal that elimination of the RF B cell clones may result in prolonged disease remission (Edwards et al, 1999).

2.4.7 Protein-A immunoadsorption therapy

Immunoadsorption is increasingly used to treat antibody-mediated autoimmune diseases. In its very basic form, it is a therapy that filters blood to remove antibodies and immune complexes that promote inflammation. Recent introduction of staphylococcal protein A (Prosorba) column, as an intervention for treatment-resistant, moderate to severe rheumatoid arthritis has prompted increased requests for this therapy by physicians and patients alike. The basis for the salutary effects of staphylococcal protein A immunoadsorption remains obscure. Because the column becomes saturated after removal of only ~1 gm of IgG, its efficacy clearly is not based on quantitative immunoglobulin depletion. Instead, an immunomodulatory effect is believed to occur, resulting from alterations in circulating immune complexes (Kiss, 2000). Column treatment appears to reduce the population of small molecular weight circulating immune complexes. These circulating immune complexes may interfere with antigen presentation to T-helper cells, thus blocking the formation of "protective" antibodies involved in immune clearance (Kiss, 2000). Circulating immune complexes may also inhibit the formation of anti-idiotypic

antibodies, which down-regulate autoantibody responses. Felson et al. studied the efficacy of SPA column treatment in comparison to a control group who received apheresis without column plasma perfusion (i.e., a sham arm) in a randomized double-blind study and his trial (Felson et al, 1999) reported that staphylococcal protein A column therapy was efficacious in patients with RA with 31.9% of 47 patients in the SPA group experiencing improvement in comparison to 11.4% in the control group ($P=0.019$). However, it appears that appropriate patient selection is essential. In general, it is recommended that such patients should be refractory to standard modes of therapy, and a risk versus benefit versus cost metric should be carefully considered.

3. Burden of illness

In economic terms, arthritis accounts for a substantial proportion of the overall economic burden of illness in society (Goetzel et al, 2004). The burden of illness is more evident in the more numerous musculo-skeletal conditions, including back pain and osteoarthritis, where there has been documented limited therapeutic progress leading to a much bigger global impact on national health and social and economic spending. Further, the less readily pathologically classifiable disorders, such as chronic pain syndromes and disability itself, remain areas of unmet need and huge economic impact.

Some evidence indicates that comorbid depression interacts with physical illness to amplify the expected level of disability associated with physical disability (Katon et al, 2002). Hansen et al (2002) demonstrated that mentally disordered medical inpatients use health care more heavily than patients without mental health problems, even after adjusting for medical disease severity. Depression is one of the major challenges facing clinical medicine. Unipolar depression was ranked fifth among the leading causes of disability worldwide in 2000 and projections indicate that by 2020 it will be ranked second only to ischemic heart disease (Murray et al, 1997). In addition to negative health consequences, depression may contribute to unemployment, loss of work productivity, and increased health care costs in persons with arthritis (Li et al, 2006). The association between these two conditions has particular relevance in the elderly population, where a substantial proportion of the burden of depression is related to chronic physical illnesses, including arthritis, which has an attributable risk of 18.1% (95% confidence interval, 9.9-25.6%) (Dunlop et al, 2004). It is unclear whether indirect costs exceed direct medical costs overall, although it appears that patients and families, rather than health care services, incur a majority of the economic costs early in disease.

Norbert Schmitz and his team (2007) recently examined the synergistic effect of depression and chronic conditions on disability. The results of this population-based study demonstrated that arthritis/rheumatism represented one of the leading disability category at 16, 8%, second only to "back problems" group. The presence of depression substantially increased the number of disability days, e.g. depression increased the Odds Ratio for functional disability from 2.1 in chronic conditions to 6.3 in chronic conditions with comorbid depression.

3.1 Psychiatric morbidity in Rheumatoid Arthritis

Medical illness and major depression co-occur at high levels in epidemiological and clinical settings. Thus, while the prevalence of depression in nonmedical populations is estimated to be between 5% and 10% in primary care (Simon et al, 2002) and at 8 - 15% in hospital-based

studies (Hansen et al, 2001), it is clear that medical diagnosis increases the risk for depression. Rheumatoid arthritis is associated with significant psychiatric morbidity that is often perceived, as surprisingly high. For example, Wells et al (1988) reported a lifetime psychiatric prevalence rate of 64% and a recent 6 months prevalence rate of 42% in patients with arthritis drawn from a community sample. Depression is one of the most common psychiatric conditions found in patients with arthritis: between 14% and 46% of patients with rheumatoid arthritis also fulfil the diagnostic criteria for depression (Zaphiropoulos et al, 1974; Frank et al, 1988; Creed et al, 1990; Hawley et al, 1993; Katz et al, 1993; Abdel-Nasser et al, 1998; Soderlin et al, 2000).

Patients are very likely to have difficulty with depression while managing their arthritis. In contradiction to the needs of this patient group, all of the above cited studies demonstrate that depression is universally associated with disability and that the detection of mental disorders and the rates of psychiatric referral and treatment are extremely low.

Depression includes a spectrum of disorders that vary in severity and associated disability. Patients with a history of major depression typically have a chronic course that requires comprehensive assessment, effective monitoring and management. Chronic depression may exist independently of, but can also be exacerbated by, disease flare-ups and other illness-related obstacles. Moderate to severe depression can adversely affect health outcomes and quality of life in a manner similar to that of other chronic medical conditions. In addition, depression may contribute to inflammation, interfere with medical adherence, and thus compromise medical treatment and management. In this regard, a longitudinal study by Ang et al (2005) found that clinical depression resulted in a 2-fold increase in the likelihood of early mortality in a cohort of patients with RA followed over a 12-year period. All of these factors heighten the importance of detecting and managing depression in patients with arthritis. When rheumatologists do not recognise depression, the risks to patients, their families, and the health care system can be severe.

In light of the above findings, the article by Sleath et al (2008) provides evidence of a significant clinical problem in the care of patients with RA. Although depression in primary care has been well studied, no studies have examined whether rheumatologists and RA patients discuss depression during medical visits. This study by Sleath et al, included 200 RA patients from four rheumatology clinics with eight participating doctors. Patient visits were audiotaped and patients were interviewed after their medical visits using a questionnaire to measure their mental status. The results showed that almost 11% of the patients in the study had moderately severe to severe symptoms of depression and that those who were rated as being more restricted in their normal activities were significantly more likely to have these symptoms. Furthermore, only 1 in 5 of the patients who showed symptoms discussed depression with their rheumatologists and they were always the ones to bring up the topic. Even when depression was brought up, it was often not discussed at any length. Several important findings stand out in this research. First, the authors found that patients who were rated by their rheumatologists as having worse functional status were more than twice as likely to have moderately severe to severe depression. Second, only 19% of the depressed patients had the opportunity to discuss their depression during medical visits. Third, when depression was addressed, the patient initiated the discussion each time. Not once during 200 office visits did a rheumatologist bring up the topic of depression to the patient. Because the study focused only on moderately severe to severe depression, the prevalence of minor depression was not assessed. Many more patients could have been afflicted with less severe forms of depression in the sample. Lastly, when patients

visit their rheumatologists, their main focus is their RA, yet such chronic diseases can greatly impact a patient's psychosocial well-being. For these reasons the authors suggest that it is important for rheumatologists to consider addressing both the RA and the depression when they see their patients. The authors note that some physicians may not feel comfortable discussing depression with their patients and advocate the use of brief depression screening questionnaires before the patient's visits in order to identify problems early on.

The prevalence of anxiety has been less well studied in this population (Soderlin et al, 2000; VanDyke et al, 2004), though there is some evidence that anxiety may be even more common than depression (El-Miedany et al, 2002), a conservative estimates of the prevalence of co-existing somatic disorders and phobias, according to Hansen's study was 12.9%.

Psychiatric syndromes have significant implications for patients with rheumatoid arthritis: individuals with both arthritis and depression report increased functional disability (Vali et al, 1998) and increased levels of arthritis-related pain (Fifield et al, 1998), compared to individuals with arthritis alone. The importance of depression is further underlined by Timonen et al (2003), who reported that 90% of females with rheumatoid arthritis who committed suicide had suffered from a depressive disorder prior to suicide. It is known that the combination of depression and physical illness is associated with small increase in suicide risk, but it increases where pain is a significant part of clinical picture, especially in the elderly.

3.2 Coping

Coping has been shown to have a strong association with response and adjustment to chronic illness, including arthritis, (Jensen et al, 1991; Becker et al, 2000) and as such play an important role in mediating the impact of disease activity. Coping is a general concept used to describe the cognitive, emotional and behavioural reactions to the challenging and distressing situations and events. The two questions in relation to coping styles have received rigorous attention: first, how an individual copes with the stresses of having a chronic illness, and second, why individuals faced with essentially the same stressful events may vary so significantly in their ability to adjust. A tentative answer to the two questions posed lies in realisation that just as competent immune system heals by altering bodily equilibrium, so do adaptive coping mechanisms reduce stress by influencing subjective perception of one's condition. Different coping strategies are not in themselves good or bad and all may serve a useful function at various times of illness and in particular circumstances. Active and passive coping refer to the degree of internal and external control, respectively, that a patient relies on to manage the consequences of a disease. Research generally concludes that, overall, strategies involving denial, catastrophizing, avoidance of activity and wishful thinking are less positive for individuals' well being than problem-focused or avoidance-orientated coping. Coping effectiveness is defined by its outcome and usually measured by the level of distress, health-related disability, or other symptomatology. To illustrate this point Brown and Nicassio (Brown & Nicassio, 1987) studied a sample of 361 rheumatoid arthritis patients and found that passive coping was associated with greater pain, disability and depression, whereas active coping was associated with less pain, disability and depression.

Within the broader classification system that categorises coping strategies as operating principally along an engagement (e.g., approach, confrontive) versus disengagement (e.g., avoidance, escape) continuum (Carver et al., 1989; Krohne, 1996; Tobin et al., 1989), a number of specific coping strategies have been identified.

3.2.1 Emotion-focused coping strategies

Essentially, there are conscious and intentional cognitive strategies that originate in an attempt to combat emotional distress, such as distraction, 'shutting down' and passive avoidance on one hand, looking for sympathy, turning to religious faith and positive reappraisal on the other. Endler and Parker (1990) describe emotion-orientated coping as comprising emotional reactions that are self-orientated but that may actually increase stress levels since they fail to actively reduce stress and may instead heighten the negative emotional component of the stress experience. Examples of such maladaptive reactions include blaming oneself for being too emotional, worrying about what one is going to do, or getting angry.

3.2.2 Problem-focused coping strategies or task-orientated coping

There are the ways in which individuals consciously seek social support and elicit help from others: direct action, confrontation, planning and information seeking are all examples of this group. It involves using a problem-solving approach to eliminate stressors. For example, perceiving a demanding schedule as being stressful and deciding to use time management skills as a means to prioritise one's demands would be an example of task-orientated coping.

3.2.3 Avoidance-orientated coping

The coping strategies that are based on distraction and social diversion are characterised here. This coping style involves turning away from the stressors, possibly by ignoring it, psychologically distancing oneself from it, or engaging in another task. An avoidance coping style may not effectively eliminate stress since this style of coping does not actively reduce stress. However, engaging in substitute tasks may be beneficial as a means of temporarily removing oneself from stress until a patient is more able to actively face stress issues and implement a task-orientated coping style (Endler & Parker, 1990). Recent research findings have suggested that the use of an avoidance-orientated coping style may serve a protective function for individuals that are in situations in which they are not able to control the stressor that they are faced with (Simon-Thomas et al, 2001). For example, children that were exposed to the stressor of parental argument (stressor that they cannot control) were found to be protected/ buffered from the effects of inter-parental conflict on child internalising behaviours if they engaged in avoidance-orientated coping. Thus, depending upon the nature of the stressor, avoidance-orientated coping may be seen as either maladaptive or adaptive.

3.2.4 Adaptive involuntary coping strategies

Defence mechanisms reduce conflict and cognitive dissonance during sudden changes in reality caused by the illness. If such changes are not adjusted for they can result in disabling anxiety and depression. Adaptive defences operate in a hierarchical way: through distortion or denial (immature defence level), repression, intellectualisation and reaction formation (intermediate defences), or at a higher adaptive level through self-assertion, affiliation, sublimation and humour.

3.2.5 Coping hierarchy

With the advent of measures that sought to investigate the nature, structure, and correlates of coping, theoreticians and researchers alike have begun to shift their views to focus more

on the hierarchical nature of coping. Three broad levels have been implicated: (a) coping styles that reflect global, dispositional, macroanalytic tendencies (e.g., monitoring-blunting, vigilance-avoidance, approach-avoidance); (b) coping strategies or modes that reflect an intermediate level in this hierarchy, and are typically indicated by summative scores on coping scales (e.g., confrontation, seeking social support, planful problem solving); and (c) coping acts or behaviors that reflect specific, situation-determined, microanalytic responses that are often indicated by individual item endorsement on a coping scale (Endler & Parker, 1990; Krohne, 1996; Schwarzer & Schwarzer, 1996).

The literature on coping with chronic illnesses and disabilities has, likewise, generated much insight into the nature and structure of coping efforts directed at diffusing or removing the stress engendered by the associated trauma, loss, and pain. Results from these and other studies strongly suggest that coping plays a significant role during the process of psychosocial adaptation to both sudden and gradual onset of chronic illnesses and disabilities. More specifically, these results indicate that: (a) a wide range of coping efforts has been employed by persons with disabilities to deal with the stresses engendered by their conditions; (b) these numerous efforts, both problem-solving and emotional-focused coping, as well as engagement- and disengagement- type coping have been found to be adaptive; (c) different coping efforts assume different roles and are, therefore, differentially employed to regulate stressful emotions and solve problems during the adaptation process; (d) coping efforts have played both a direct role (i.e., are directly linked to measures of psychosocial adaptation to disability) and a mediator role (i.e., act as mediators between sociodemographic variables, personality attributes, disability-related factors, environmental conditions, and outcomes of psychosocial adaptation); and (e) different disabling conditions imply different functional (e.g., mobility, manipulation, fatigue, cognitive) limitations, medical courses and prognostic indicators (e.g., deteriorating, unpredictable, stable), related health problems, treatment modalities, and psychosocial reactions. Individuals cognitively appraise the situation in terms of its personal significance, and then look at the resources and options they have available. This notion helps to appreciate the variability in individual coping reactions. The coping strategies adopted by an individual are quite unique; they include the way one perceives threatening experiences and reacts to stressful events, how one manages one's emotions and how one attempts to solve problems.

3.2.6 Age and gender differences

The effectiveness of coping strategies across the lifespan has been another area of clinical interest. Contrary to suggested belief that individuals become less efficient at coping with the demands of life as they get older, research into success of coping revealed immunity to the age process. Thus, in a recent study investigating age variance in coping across a broad range of stressors in a sample of more than 2,000 men ranging in age from the late 40s to over 90, there were no significant age differences in the reporting of negative emotional states in response to stressors, nor perceived efficacy in coping (Dunkin & Amano, 2005).

In relation to gender differences, women appear to report positive and negative affects more vividly than men. In one study (Diener et al, 1999), gender accounted for 13 percent of the variance of the intensity of reported emotional experiences. There is also considerable evidence that women are more likely to use formal helping systems than are other groups, especially men and people of colour. One recent study addressed the natural coping systems of male and female students in largely young, Euro-American sample (Slattery et al, 2002).

They found significant gender-specific pattern in the use of coping strategies and their perceived effectiveness. The authors reported that females were significantly more likely than males to seek appropriate help and try to solve the problem, but also to use eating, cleaning, shopping, crying and praying. Interestingly enough, males were more likely to report using sex and masturbation in their attempt to cope than females. Both sexes described avoiding others, doing nothing, and ignoring the problem as least helpful.

3.2.7 Cultural aspects of coping

Cultural aspects of coping emerge as a new dimension in the ethnically diverse world today. Native Americans, for example, tend to turn to spiritual leaders and extended family (informal helping system) rather than to formal helping systems such as therapists (LaFramboisie, 2000). Similar findings have been reported for African Americans and Hispanic cultures (Sue & Sue, 1997); in England the Government's race equality strategy (Department of Health UK, 2003) have illustrated how local African community avoid statutory care systems and try to contain problems in their homes long beyond the expected point of seeking outside help. This could be a result of natural difficulty with disclosing problems or sharing emotions in this group or inadequacy of existing services to address their psychological needs. In his timely review Brendan Kelly (Kelly, 2003) highlighted that globalisation and large-scale social changes could induce a wave of 'anomie' in migrants, that is in essence a breakdown of social values (Durkheim, 1947). For Durkheim, in 1897 anomie arised more generally from a mismatch between personal or group standards and wider social standards, or from the lack of a social ethic, which produced moral deregulation and an absence of legitimate aspirations. For migrants living in a state where societal standing is compromised and social ties are broken, anomie becomes a nurtured condition that has detrimental effects on their coping capacity.

3.3 Illness perception

Patients do not respond to treatment in a predictable manner and show a wide variation in perception of causation. Individual preconceptions determine help seeking, compliance and treatment outcome, yet clinicians rarely explore these issues. Early exploration of illness perceptions may enhance health behaviour and maximise the impact of intervention.

Lay illness representations often diverge from the clinician's understanding of the presenting problem and strongly influence treatment behaviour. Perception of the significance of decline in social functioning, including some losses in valued activities, which an individual regards as being important, e.g. visiting the family, going away on holiday is an important factor that only recently has been emphasised by Katz & Yelin (1995). In their 4-yr longitudinal study they found that patients' perception of a decline in valued activities by 10% was followed by a seven-fold increase in depression over the subsequent year. The self-regulation model (Leventhal et al, 1980) suggests that the cognitive and emotional aspects of illness perception guide the response to illness and determine the effectiveness of coping. Furthermore, five components of illness perception have been recognised: the identity of the illness (i.e., the symptoms and their labels); the perceived consequences of the illness; the illness's causation; its likely time line and the potential for control and cure (Lau et al, 1989).

Studies investigating the relationship between illness perceptions and coping show that the way affected people deal with their illness has great influence on their physical and

psychological wellbeing. Much of this work has focused on the health and wellbeing of chronically ill patients with musculoskeletal illnesses such as rheumatoid arthritis. Scharloo and colleagues (Scharloo et al, 1998) presented data showing that patients with rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis achieve significantly better functioning when cope by seeking social support and believe in controllability and curability of the disease. Support from family and close companions can help to increase individual's sense of control of their symptoms, as this kind of empowerment helps people act on their own behalf in relation to their dealings with RA (Delzell, 2011).

4. Conclusion

While today we celebrate the advances in clinical science and in therapeutics, the enigmatic nature of RA still gives way to conceptualisation disparity. Indeed, despite some significant gains in the areas of immunopathology and genetics, Landré Beauvais' first clinical description of rheumatoid arthritis in 1800 encompasses most of what we know about this disease today. Where no single factor can provide a satisfactory explanation of a disorder in question, the biopsychosocial approach helps to position the multiple layers of existing knowledge in relation to it. Laboratory studies of inflammation and genetics provide the scientific basis of mainstream treatments, although the speciality still lacks good clinical and laboratory markers for making prognosis in each individual case.

In conclusion, our predecessors are to be congratulated for providing a platform for future developments. There are compelling data to suggest that the combination of earlier use of disease modifying treatments, attention to coexisting conditions and patient's coping and illness perception, that are considered to be important contributing factors in the relationship between physical and psychological factors in RA. The evolution and refinement of the newer therapies will allow more patients to realistically strive for disease remission and return of function in the near future. Rheumatologists of tomorrow are to be encouraged to carefully sift through the complex information generated during assessment process and to focus clinical and therapeutic developments where they can best be translated into better care for those with this taxing disease.

5. References

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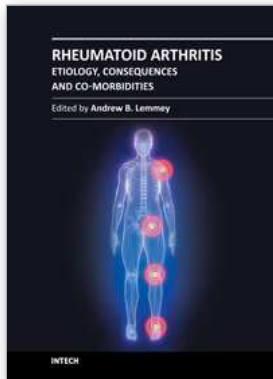
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 16 chapters, with contributions from numerous countries (e.g. UK, USA, Japan, Sweden, Spain, Ireland, Poland, Norway), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Etiology, Consequences and Co-Morbidities will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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