

## From the Desk of Former Editor



# Rheumatology, Past, Present and Future

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“Medical historians do need to remember that the content of medical knowledge ought not to be buried beside the great men”.

*C. Boyce. Lancet 2011; 378 : 655-56*

“..... the knowledge which is your privilege today to acquire so early has cost others. We are, all of us, debtors to our profession”

*William Osler<sup>1</sup>*

Musculoskeletal disorders (MSD) are likely as old as the hominids. The first recorded evidence of MSD appears in Ebers Papyrus written around 1500 BC. It describes what appears to be arthritis deformans (probably rheumatoid arthritis - RA). Paleopathological studies of Egyptian mummies suggest existence of RA in Egyptians. G. Elliot based on his studies, concluded that RA was par excellence the disease of Egyptians.<sup>2</sup> Many authorities, however, do not agree and consider RA to be a modern disease.

In the Indian literature, Charak Samhita (approx 300 – 200 BC)<sup>3</sup> describes pain, joint swelling and loss of function.<sup>3</sup> In a recent reappraisal Aceves-Avila et al – claim that RA is an old disease.<sup>4</sup>

Hippocrates described arthritis 2400 years back (400 BC). For a long time the term arthritis was used loosely without reference to any specific form of arthritis.

Galen (129-216 AD) introduced the term rheumatismus. Camroe (1940) coined the term rheumatologist while the word rheumatology appears for the first time in the text book by Hollander (1949).<sup>5</sup>

Rheumatic disorders were attributed to humors (rheuma). It was postulated that a substance i.e. humor, flows, settles in joints, and causes arthritis. Paracelsus (1493-1511) postulated that substances that could not be passed in urine accumulated, got precipitated in joints, and caused arthritis. Ayurveda considered arthritis as one of the Vata.

Since then, rheumatology has come a long-longway. It is no more an “also branch” of medicine. No more is a rheumatologist questioned “but what can you do ?” There is today virtually no branch of internal medicine that probably does not interact with rheumatology. The present article attempts a brief review of evolution (history) of rheumatology upto the present time and peeps into (read dreams) the future.

## The Rheumatic Diseases

“A disease is born when named”

Slowly but surely from the all pervasive diagnosis of arthritis individual disease entities have been recognized. Presently more than 100 specific rheumatic diseases are known. There surely are more to be defined.

\*The exact period is disputed with some claiming it to be 2000 BC or even earlier

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Amongst the first to be defined were gout, rheumatoid arthritis, osteoarthritis, and rheumatic fever.

### Rheumatoid arthritis<sup>2,5,6</sup>

Thomas Sydenham had recognized a crippling form of chronic arthritis, (most likely rheumatoid arthritis). Londre’ – Beauvais (1880) most likely also described it. Brodie pointed out its chronic progressive course and noted that tendon sheaths and bursae can be affected. Further, he recognized that the disease begins as synovitis and cartilage damage may follow. A B Garrod (1858) coined the term rheumatoid arthritis (RA) replacing the old terms arthritis deformans and rheumatic gout. To him goes the credit of clearly separating rheumatoid arthritis from osteoarthritis and gout. The radiologic features of RA were first described by Bannatyne (1896).

### Gout<sup>5</sup>

The credit of much that we know of gout goes to Alfred B Garrod. Before him, Leeuwenhoek (the father of microbiology) had described microscopic appearance of urate crystals (1634) and Sydenham had vividly described acute attack of gout, himself being a sufferer. The contributions of Garrod are i) quantitative assay (gravimetric) to detect hyperuricaemia (1847) ii) thread test to demonstrate urate crystals (1854) iii) demonstration of urate crystals in joint and soft tissues iv) postulating that hyperuricaemia may be the result of overproduction or under excretion (by the kidneys) v) wrote a monogram on gout (1859).

### Osteoarthritis<sup>5</sup>

Osteoarthritis is a disease of antiquity. The term osteoarthritis was introduced by Spender in 1886. The credit for its modern connotation goes to Archibald E Garrod (1907). Much earlier (1802) Heberden had noted the nodes, (Heberden nodes) and differentiated them from tophi. Garrod identified the connection between the nodes and the joint disease. Bouchard (1884) described the nodes at proximal interphalangeal joints (Bouchard’s nodes).

### Rheumatic fever<sup>5</sup>

Hippocrates most probably had described rheumatic fever. Sydenham recognized it as a separate form of arthritis (1665). Involvement of heart was described by Dundas in 1808. He used the term rheumatic fever. Money (1883) described myocardial granulomas which Aschoff described in detail (1904) (Aschoff nodules). Chorea (Sydenham’s chorea) was described by Sydenham. Its association with rheumatic fever was noted by Bright (1831) and See (1850). Its relation with streptococcal sore throat was postulated by Swift in 1928. Collis and Coburn independently identified beta-haemolytic streptococcus as the causative bacterium (1931). The discovery of antistreptolysins by Todd completed the loop (1932).

### Spondyloarthropathies(s)<sup>7</sup>

Before the concept of spondyloarthropathy (SpA) was developed by Moll and Wright (1974) diseases like ankylosing spondylitis, psoriatic arthritis were described as variants of rheumatoid arthritis or its atypical forms. SpA is now recognized

### Box 1 : Rheumatic diseases with eponyms <sup>9</sup>

|   |   |
|---|---|
| Schonlein; 1874 Henoch (1837)<br>(Henoch Schonlein purpura) | Felty's syndrome (1934)   |
| Charcoat's joints (1868)                                    | Wegner's granulomatosis<br>(now renamed granulomatous<br>polyangiitis) (1936) |
| Jaccoud's arthropathy (1869)                                | Behcet's disease/syndrome (1937)  |
| Paget's disease of bone (1877)                              | Churg-Strauss syndrome (1939)   |
| Pott's disease (spine) (1882)                               | Cogan's syndrome (1945)   |
| Weber – Christian disease (1892)                            | Takayasu's disease<br>(arteritis) (1945)                                      |
| DeQuervain's tenosynovitis<br>(1895)                        | Caplan syndrome (1951)  |
| Poncet's disease (1897)                                     | Lofgren syndrome (1953)   |
| Still's disease (1897)                                      | Kawasaki disease (1961)   |
| Reiter's syndrome (now called<br>reactive arthritis) (1916) | Sweet syndrome (1964)   |
| Tietze's syndrome (1921)                                    | Lyme disease (1976)   |
| Libman Sachs endocarditis (1923)                            | Anti-phospholipid syndrome<br>Hughe's syndrome (1986)                         |
| Sjogren's syndrome (1933)                                   |   |

(It is a travesty of fate that many of these e.g. Reiter's syndrome, Wegner's granulomatosis were described first by others).

as a family of diseases that includes ankylosing spondylitis, psoriatic arthritis, reactive arthritis (Reiter's syndrome), arthritis associated with inflammatory bowel disease and unclassifiable SpA. The most characteristic feature of SpAs is strong association with HLA B 27 and seronegativity.

#### Systemic lupus erythematosus (SLE)<sup>8</sup>

Historically SLE dates back to middle ages. For quite some time the term 'lupus' was applied to various cutaneous lesions. Kaposi (1872) described the systemic nature of the disease and Osler (1900) firmly established the same. SLE is today "the prototype" connective tissue disorder. The concept introduced of connective tissue disorders was developed by Klemprer in 1942. Cozenove (1851) introduced the term systemic lupus erythematosus. Libman Sacks described mitral valve endocarditis (1924).

Space constraint does not permit to include the history of other rheumatic disorders. A large number of carry an eponym. (Box – 1), after the discoverer.

## Diagnostic, and Classification Criteria<sup>10</sup>

Most of the rheumatic diseases are syndromic. They lack definite diagnostic features, (clinical and investigative). It is therefore essential to have criteria that ensure uniformity of diagnosis, classification and epidemiological studies. Disease specific criteria have been developed for most of the rheumatic disorders, majority during the last 3-4 decades. These have contributed significantly to the practice and progress of rheumatology. Criteria being an evolving phenomenon are updated periodically.

## Assessment Scales and Indices<sup>11</sup>

For similar reasons criteria have been developed to assess disease activity e.g. DAS-28, (RA); SLEDAI (SLE); damage (vasculitis damage index); remission, cure (RA); function (HAQ, SF-36) and pain (visual analogue scale -VAS). These find their place not only in the research setting but also in daily

### Box 2 : Landmark developments

|   |
|---|
| Leeuwenhoek – microscopic appearance of urate crystals in a tophus (1634) |
| X-rays of rheumatoid joints – Bannatyne (1896)                            |
| Calorimetric measurement of uric acid - Folin Wu (1912)                   |
| Antistreptolysin antibodies – Todd (1932)                                 |
| Rheumatoid factor - Rose and Waaler (1940)                                |
| LE cell-Hargraves (an interesting story of serendipity) (1948)            |
| Lupus anticoagulant – Conley (1952)                                       |
| Antinuclear antibodies - Friou (1958)                                     |
| Bone densitometry – Cameron (1960)  |
| Radioimmunoassay for 25 (OH) D <sub>3</sub> – Haddad (1971)               |
| Association of HLA B 27 with AS - Schlosstein and Brewerton (1973)        |
| ANCA – Davis (1982)   |

(Despite the increasing availability and use of diagnostics, rheumatology remains a clinical speciality par excellence)

clinical practice. Disease activity indices have empowered rheumatologists to tailor/modify treatment(s) to achieve maximum disease control in an objective way and not based on mere impressions.

These activities have been formulated by national and international associations including Indian Rheumatology Association. With all these inputs the practice of rheumatology has become more scientific and objective.

## Guidelines

Guidelines of management have also been developed for most of the rheumatic diseases. These too are updated periodically.

## International initiatives

Ongoing COPCORD (Community Oriented Programme for Control of Rheumatic Diseases) and the just completed, bone and joint decade (2000-2010) have been two recent major international initiatives. COPCORD was launched in late 1980's by WHO and International League Against Rheumatism (ILAR) to collect epidemiologic data (of pain and disability), to impart health education and control the risk factors with improved health care in developing countries (grass root developing economies). World-wide, several countries have participated in this programme. These studies have highlighted the very significant burden of musculoskeletal disorders (MSD), emphasizing MSDs as measure of public health problems.<sup>12</sup>

Bone and Joint Decade (2000-2010) was supported by WHO and United Nations. Its agenda included trauma, arthritis and osteoporosis as target conditions. The aim was to create awareness and empower patients. India has been an active participant in both the initiatives.

## Diagnostics

Microbiology, including serology, biochemistry, imaging modalities, radioimmuno and other assays, genetics have been an integral part of rheumatology. Some of the important/land mark developments are listed in (Box 2)

## Molecular Biology

The edifice of modern rheumatology is based on advances in molecular biology. It is beyond the scope of this article to elaborate the immense contributions of molecular biology to rheumatology. Briefly, molecular biology has revealed that

- i. Molecular and genetic events shape diseases, their progression, and response to therapy.
- ii. Immune dysfunction (autoimmunity) forms the basis of many rheumatic diseases.
- iii. HLA and other gene polymorphisms play a role in autoimmune diseases
- iv. Immune cells, cytokines, signalling pathways and mediators of inflammation are important therapeutic targets.

## Therapeutic Milestones

Rheumatology has directly or indirectly contributed to the development of some of the most important therapeutic agents, such as NSAIDs, cortisone, sulfasalazine, and biologics.

- **NSAID**<sup>2,3,13</sup>

The earlier therapies involved use of plant extracts of Willow bark and leaves; most contained salicin. Hippocrates, Galen, and others used Willow extracts to treat pain of rheumatic disorders. Madhav nidan (7 century AD) subclassified arthritic disorders. Chakradatta in the 11<sup>th</sup> century fine tuned pharmacologic and nonpharmacologic Ayurvedic therapy. It included diet, local treatments, bowel cleansing and medicated enemas, depending upon the type of arthritis Salicylic acid was identified as the active substance by Leroux in 1929. In 1853, acetyl salicylic acid (aspirin) was synthesized by Gerhardt. The first nonaspirin, nonsteroidal anti-inflammatory drug, phenylbutazone became available in 1949 and was followed by a host of NSAIDs. Though effective, NSAIDs have significant toxicity profile, especially gastrointestinal ulcers and bleeding, renal toxicity, hypertension and oedema. Vane (1971) demonstrated that NSAIDs inhibit prostaglandin synthesis by acting on the enzyme cyclooxygenase (COX). In 1991 COX-2 (the inducible form) was discovered by Simmons and the next generation of NSAIDs (selective COX-2 inhibitors) were developed.

- **Colchicine**<sup>2</sup>

Extracted from Autumn crocus, colchicine was used to treat acute gout as far back as 6<sup>th</sup> century AD. A B Garrod established its use for the diagnosis and therapy of gout.

- **Cortisone**<sup>2</sup>

- 1930 - Kendall isolated 6 different compounds (A-F) from adrenal gland
- 1948 - Compound E was found to have anti-rheumatic properties (Kendall)
- 1948 - Hench treated the first case of rheumatoid arthritis with compound E

Today cortisone is an integral part of treatment of many inflammatory rheumatic and non rheumatic disorders (despite the love and hate relationship it generates).

- **Methotrexate**<sup>14</sup>

- *Methotrexate (MTX)* was synthesized in 1950's as a folate antagonist to treat leukaemia.
- Double-blind placebo controlled trials were carried out in 1980's. These established its role in the treatment of rheumatoid arthritis
- In 1990's the role of folic acid supplementation to reduce methotrexate toxicity was realized
- Presently MTX is the sheetanchor of treatment of RA

either as monotherapy or in combination with other agents (DMARDs and biologics)

- **Biologics**<sup>15</sup>

1975 – Monocyte derived tumour necrosis (TNF) factor was identified its role in orchestrating inflammation appreciated (1988)

1993 – Anti-TNF antibodies were shown to be effective in the treatment of patients with RA (1993). Presently there is an explosion of biologic agents that act against the many components of immune response such as cells, cytokines, and signaling pathways. While highly effective, danger of infection especially tuberculosis soon became apparent leading to the (modified) concept of diagnosis and treatment of latent tuberculosis.

Cost remains an important consideration while considering their use. Most biologics work better in combination with methotrexate.

- **Antimalarials**<sup>2,16</sup>

Payne (1895), first suggested the use of quinine to treat lupus erythematosus and rheumatic diseases. In 1951 Page demonstrated efficacy of quinacrine (mepacrine) in lupus erythematosus. This was followed by the use of chloroquine (Baguall 1957) and now hydroxychloroquine (HCQ). HCQ today is used extensively in many rheumatic diseases because of its multiple benefits, low toxicity, and low cost.

- **Gold**<sup>2,17</sup>

As far as back 2000 BC, Egyptians and Chinese used gold for medicinal purposes. In 1927 Landre had recommended its use to treat rheumatic fever.

Gold salts were first used to treat rheumatoid arthritis by Forestier (1925) on the wrong assumption of tuberculosis as its aetiological factor and gold was then used to treat tuberculosis. In the 1970's and 80's gold was the most commonly used DMARD. Presently gold salts are rarely used to treat RA because of the availability of better and safer drugs.

Steroids, methotrexate, chloroquine/hydroxychloroquine, leflunomide, sulfasalazine, mycophenolate, biologics and others (cyclosporine, azathioprine etc.) have revolutionized the outcome of rheumatic diseases.

## Change in Therapeutic Perception

Early action and aggression is the new 'Mantra' of rheumatology, especially in case of R.A. The change is -

- RA is not a benign disease
- Joint damage starts early
- The best chance to control the disease effectively is as near the disease onset as possible. The previous go slow, go low paradigm is not acceptable.
- Combination therapy is effective and not more toxic
- Complete remission is possible, (albeit at present in a small proportion of patients)

### Pulse therapy

Some examples are -

- Methotrexate in weekly pulse doses (effective and less toxic)
- Pulse cyclophosphamide treatment (Austin 1986). It has had a significant impact on the management of SLE, systemic vasculitidis, and other systemic rheumatic diseases.
- Steroid pulse therapy for rheumatic emergencies

## Surgery<sup>2</sup>

Before the advent of joint replacement therapy surgical interventions consisted mainly of synovectomy and arthrodesis for synovitis and osteotomies for osteoarthritis of knee and hip.

Hip joint replacement, developed by Charnley, (1961) changed it all. Joint replacement has proven to be a boon to patients with advanced joint disease, unbearable pain, and disability. Newer models have increased the range of joint motion, improved function (squatting and negotiating stairs is possible with modern prosthesis) and longevity of the prosthesis.

Historically Gluck (1853-1942) had suggested knee replacement with implants made of ivory and metal and carried out joint replacement in joint tuberculosis and tumours (of hip, knee, shoulder, elbow and wrist) !

## Support service

Ever improving orthotics, physiotherapy, nutrition and formation of support groups have in no small measure contributed to improved patient care (especially in the more advanced countries).

## Future – Crystal-ball Gazing

The wish list is large. A few expectations are

- Effective preventive measures
- Vaccination
- Preclinical diagnosis of rheumatic diseases
- Magic bullets

There is great hope that most if not all can be achieved in the present century itself –

Specifically for India one hopes

- Availability of rheumatologist (at least one) in each district
- Availability of cheap and effective therapeutic agents including surgical implants
- Scientific evaluation of systems of medicine especially Ayurveda
- Public education and awareness. Today there is unfortunately a plethora of misconceptions and blind faith

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