Managing rheumatic and musculoskeletal diseases:

Past, present and future

Gerd R. Burmester (also for correspondence)
Department of Rheumatology and Clinical Immunology
Charité - University Medicine Berlin
Charitéplatz 1, D - 10117 Berlin
Germany

Johannes W. J. Bijlsma
Department of Rheumatology and Clinical Immunology
University Medical Center Utrecht
Box 85 500 3508CX Utrecht
The Netherlands

Maurizio Cutolo
Research Laboratory and Academic Division of Clinical Rheumatology,
Department of Internal Medicine,
University of Genova
Italy

Iain B. McInnes
Institute of Infection, Immunity and Inflammation,
College of Medical, Veterinary and Life Sciences,
University of Glasgow,
120 University Place,
Glasgow, G12 8TA

Abstract

Progress in rheumatology has been remarkable in the last 70 years impacting favourably on quality of life for people with rheumatic and musculoskeletal diseases. Therapeutics have advanced from early developments including the introduction of glucocorticoids, the general use of methotrexate and other disease modifying agents, through to the advent of biologic and recently small molecule JAK-inhibitors. Strategic approaches using such agents also transformed outcomes. Similarly, non-pharmacologic management of RMDs including surgery, physical and occupational therapy have contributed greatly to progress delivered within the multi-disciplinary team. Breakthroughs in pathogenesis understanding, diagnostics, and the use of 'big data' continue to drive the field. Critically, and especially going forward, the patient is at the centre of management strategies and the future research agenda.

Introduction

Rheumatology is one of the most fascinating and comprehensive disciplines in medicine. Few medical specialties have matched the rate of progress in understanding disease pathogenesis leading to novel therapeutic development. When combined with innovations in the strategic approach to care embodied in the "Treat to Target" concept that aims for remission employing constant monitoring and adaptation of treatments, this has led to a transformation of outcomes for patients. Progress has been especially remarkable across diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) providing a blueprint for similar developments in the wider spectrum of rheumatologic conditions. However, even previously often fatal diseases such as severe systemic lupus erythematosus (SLE) or granulomatosis with polyangiitis (GPA) can now be managed by modern immunosuppressive therapies to better outcome. Nevertheless, there are significant unmet medical needs, especially in the connective tissues disease spectrum, e.g. systemic sclerosis, in osteoarthritis

(OA) and in fibromyalgia where we frequently lack effective drug treatments. On the occasion of the 70th anniversary of the European League Against Rheumatology (EULAR) (see box), the major rheumatologic association of physicians/scientists, health professionals and people with rheumatic and musculoskeletal diseases (RMDs) in Europe, it is timely to reflect on our past, our present and our remaining future challenges.

Box

In 1913 the Dutch general practitioner Jan van Breemen, moved by the needs of disabled people in his practice, initiated an international cooperative to fight rheumatic and musculoskeletal diseases (RMDs). His initiative to form an International Organisation for the Investigation of Rheumatic Diseases was delayed by World War 1 until 1919. In 1925 this organisation transformed into the International League Against Rheumatism (ILAR). ILAR aims were: *to stimulate and promote the development of awareness, knowledge and means of prevention, treatment, rehabilitation, and the relief of rheumatic diseases; to foster co-operation between different countries and regions concerned with the objectives of ILAR; to encourage and assist in the creation of rheumatism societies in areas of the world where they do not exist*[1]. Aligned with these aims, regional Leagues were formed, namely PANLAR in the Pan-American Region in 1943, and EULAR in the European region in 1947, that included some non-European countries, e.g. in North-Africa that in 1989 joined the African League (AFLAR). Later the Asia Pacific League of Associations for Rheumatology (APLAR) was established in Sydney in 1963.

The first EULAR Congress was held 70 years ago in September 1947 in Copenhagen and was attended by 200 delegates from 16 countries. At the EULAR 2017 Madrid Congress about 14,000 attendees are expected, coming from more than 120 countries. EULAR has in these 70 years developed into a unique organisation of rheumatologists, scientists, health professionals

and patients, arising from 45 countries, who together aim *to reduce the burden of rheumatic diseases on the individual and society and to improve the treatment, prevention and rehabilitation of musculoskeletal diseases. To this end, EULAR fosters excellence in education and research in the field of rheumatology. It promotes translation of research advances into daily care and fights for the recognition of the needs of people with RMDs by the governing bodies in Europe* (EULAR mission statement 2005, http://www.eular.org/eular_mission.cfm)

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70 Years of treatment of RMDs

Pharmacological treatment:

Pharmacologic therapeutics for RMDs have evolved remarkably over these 70 years. The earliest clinical use of *glucocorticoids* (GCs) more than half a century ago in a bedridden RA patient (1948) prompted a 'miraculous' recovery that was the first break-through in the treatment of RA. Two years later (1950) the Nobel Prize was given for this discovery. GCs have been part of the treatment of nearly all inflammatory RMDs since. GCs have many beneficial effects (e.g. life-saving in nephritis), but also detrimental effects (e.g. death through masked infections). Their safety has been debated; presently there is consensus that long-term use of doses of 5 mg prednisone or below/day is rather safe, while long-term use of doses of 10 mg prednisone or above/day is in general not advised[2].

Conventional disease modifying anti-rheumatic drugs:

Sulfasalazine was formulated in 1942 by the Swedish Nana Svartz[3] as a combination of sulfapyridine and 5-amino salicylic acid, with the assumption that the antibiotic (sulfonamide) would benefit the presumed infective component and the salicylate the pain and stiffness component of polyarthritis. It is now used in RA, especially as a component of triple therapy, but perhaps most in peripheral spondyloarthritis.

Methotrexate (MTX) was developed in 1946, but the first publications of its use in RA date to nearly 40 years later[4]. It was initially used especially in patients with psoriatic arthritis, since the skin lesions responded very well to MTX. Only after starting to use higher dosages of MTX (up to 25 mg/week) did the real potential of MTX in the treatment of RA emerge[5]. Nowadays both GCs and MTX are considered the "anchor drugs" in the treatment of RA[6]. In many other inflammatory RMDs MTX has found its place as a potent immune-suppressive drug, often enabling a decrease of the dosage GCs that patients´ need[7].

Other csDMARDS

A variety of other DMARDs also found their place in the treatment especially of inflammatory arthropathies e.g. gold, D-penicillamine, auranofin, cyclosporine A or leflunomide, the last an alternative to the treatment of RA in case of MTX failure or contraindications. This phase of RMD treatment was remarkable for the narrow toxicity benefit windows that were pervasive and dominated clinical practice – and in turn lead to a conservative approach to care, often leading to delays in the commencement of effective therapeutics to long term detriment. The observation that combinations of these agents conferred advantage without necessarily increasing toxicity was a seminal advance. Moreover these agents were also used to establish the principle that early intervention was preferable and that targeted treatment goals could also dramatically improve outcomes[8].

Biologicals delivered a further step-change for patients with RMDs. Targeted as a result of elegant pathogenesis discovery, Tumor Necrosis Factor alpha (TNF) inhibition in patients with RA[9] and then also in patients with spondyloarthritides, psoriasis and Juvenile Idiopathic Arthritis provided critical proof of concept that immune targeting capitalising on exquisite specificity of monoclonal antibodies and other biotechnical developments could deliver in the clinic. Biologicals with other mechanisms of action (against Interleukin-1, IL-6, IL-17, depleting B-cells, interfering with co-stimulation molecules or intracellular signalling like

kinase inhibitors) have followed and are generally effective in an increasing range of RMDs, including system autoimmune diseases, gout and osteoporosis[10]. Biologicals were a non-existing market in the 90s, but have now grown to a market well over 100 billion Euros a year[11]. In addition, starting (aggressive) treatment in inflammatory RMDs early has been widely adopted and lead to a significant gain in efficacy, and drug free remission is now becoming an attainable goal in the treatment of RA[12]. A timeline of drug development in rheumatology is presented in Figure 1.

Surgical treatment

Total joint replacement has become the treatment of ultimate choice in patients with osteoarthritis of the hip and knee. Many joints are amenable to replacement in RMDs, sometimes aided by 3D evaluation and printing. Total joint replacement is one of the most frequent and cost-effective surgical interventions worldwide[13]. Interestingly, although previously commonly used for many patients with RA, with improved medical treatment, the necessity for such interventions has become rarer. There are interesting new developments in the surgical approach to resolving articular problems, especially in different phases of osteoarthritis including e.g. resurfacing operations; joint distraction in relatively young patients (45-60 years)[14], thus postponing a total joint replacement; mesenchymal stem cell transplantation in localised (often traumatic) osteoarthritic cartilage lesions and others[15]. Minimal invasive surgical methods are presently under development to treat future RMD-patients.

Non-Pharmacological treatment

At the celebration of 50 years of non-physician health professionals in Rheumatology[16] three Science-driven Practice Paradigm Shifts were recognized that now play an important role in

managing patients with RMDs. Widely used "Self-management programs", were developed from information giving and 'patient education'. The positive and intensive use of "Exercise and physical activity" was developed from previous acclaimed bed rest and assisted range of motion exercises. Finally, OMERACT initiated definitions and applications of Patient-Reported Outcome measures, instead of only biomedical assessment of disease activity. In addition, two 'Evolutions in Practice' were recognized. Understanding Psychological Factors, from accepting "the arthritic personality" to actively addressing depression, anxiety, coping skills, sense of control and confidence. In addition the implementation of important rules for nurses and other health professionals as supported by EULAR strategic plans have improved the management of patients with RMD[6].

Patients' perspectives and involvement

When asked, patients clearly recognize that the evolution of research and scientific knowledge has enabled a new era of treatment for people with RMDs and has made remission possible for many patients[17]. Here the experience of the EULAR patients associations (PAREs) has become a "driving force" in the last decades.

Important breakthroughs include wider adoption of information dissemination and self-management to support a better outcome for patient. Patient participation in research adds the patients' views and contributes to successful study design and outcome dissemination and implementation. Finally there is a growing awareness that shared decision making means a therapeutic gain

70 Years development of diagnostics in rheumatic diseases: laboratory analyses and imaging techniques

From rheumatoid factors to anti-citrullinated protein/peptide antibodies

Two years after EULAR was founded, Rose redescribed in 1949 the test for **rheumatoid factors** which had been discovered by the Norwegian Erik Waaler in 1937[18]. He was among the founders of EULAR in 1947. The subsequently developed Waaler-Rose test used sensitized sheep erythrocytes to detect rheumatoid factors but is now replaced by nephelometry or ideally an ELISA system which can detect RFs of various immunoglobulin isotypes. Twenty four years later, Nienhuis et al. detected a novel antibody specificity which they called the anti-perinuclear factor (APF) identifying keratohyalin granules in buccal mucosa cells (reviewed in[19]). 15 years later anti-keratin antibodies (AKA) were reported, which were RA specific and reacted with keratinized tissues of the oesophagus and interestingly also with cells from human hair follicles. In 1993, filaggrin was described to be recognized by RA sera, and subsequently it was shown that both APF and AKA reacted with (pro)fillagrin proteins (present in the keratohyalin granules in terminally differentiated epidermal cells) and were then named anti-filaggrin antibodies (AFA). A major breakthrough was the detection of the enzyme peptidyl-arginine deiminase (PAD) responsible for the citrullination of molecules which subsequently may become immunogenic to the RA immune system, e.g. citrullinated filaggrin, but also with many other molecules such as vimentin, collagen and enolase. They were then termed **ACPA (anti-citrullinated protein/peptide antibodies**). All these findings led to new test systems to detect anti-citrullinated protein/peptide antibodies including the anti-ccp (cyclic citrullinated peptides) test, and others such as the MCV (modified citrullinated vimentin) test followed. Finally in 2010, both the RF and ACPA became important corner stones in the ACR/EULAR RA classification criteria[20].

Other posttranslational modifications such as carbamylation have also been shown to render proteins immunogenic in RA[21], and there may be a possible link between the induction of RF and carbamylated proteins[22].

Other milestones in laboratory diagnosis concerned the detection of "LE cells" by Hargraves and colleagues in 1948[23], and subsequently an inducing factor was found in the serum of SLE patients. In 1953, Miescher observed that rabbit sera induced the SLE cell formation after immunization with human leukocytes and could finally demonstrate that nuclei from calf thymus cells led to the elimination of the LE cell phenomenon[24]. Thus, the LE factor was identified as **antinuclear antibodies (ANA)**. Subsequently, DNA was detected as the responsible antigen and then numerous other autoantibody specificities against nuclear antigens that were present in salt-soluble extracts from calf thymus cells (called extractable nuclear antigens, **ENA**) have been detected[25]. Another major breakthrough was the detection of the **anti-neutrophil cytoplasmic antibodies** (ANCA) in 1985 by van der Woude et al. which greatly helped in the diagnosis and management of vasculitides[26].

Imaging and RMDs

Besides a laboratory work up, imaging procedures are important tools to diagnose and monitor rheumatic diseases. Conventional **x-rays** were detected in 1895 by the Nobel laureate Wilhelm C. Röntgen, a German mechanical engineer, and the first x-ray of a hand was shown in 1896[27]. This technique revolutionized the diagnostic procedures in RMDs. In rheumatology, a major breakthrough was the scoring of x-ray changes such as the Larsen score in 1977[28] and the Sharp score in 1985[29], which was then modified by van der Heijde et al. in 1989[30]. These scores enabled the assessment of structural damage for instance in RA and guided the design of many modern trials providing evidence of halting progression by modern treatment.

In 1959, the neurologist William Oldendorf developed the idea of "scanning a head through a transmitted beam of X-rays, and being able to reconstruct the radiodensity patterns of a plane through the head" triggered by seeing an automated apparatus built to reject frostbitten fruits by detecting dehydrated portions. In 1961, he described the basic tomography concept[31], which was later used by McLeod Cormack to develop the mathematics behind the CT technology[32]. Transverse axial scanning was then due in large part to the work of Hounsfield and McLeod Cormack who received in 1979 the Nobel Prize in Physiology and Medicine "for the development of computer assisted tomography". In rheumatology, this technique is used in many areas ranging from the assessment of lung involvement in systemic autoimmune diseases to the evaluation crystal dispositions in gout using dual emission CT (DECT), and finally to detect finger joint erosions in micro CT.

Magnetic resonance imaging (MRI)[33] represents a further pivotal development that allows evaluation of soft tissues based on measurement of relaxation, diffusion, and chemical exchange of water in cells and tissues. Paul Lauterbur at Stony Brook University developed a way to generate the first MRI images and published the first nuclear MRI in 1973 and the first cross-sectional image of a living mouse in January 1974. In the late 1970s, Peter Mansfield developed a new technique that led to scans taking seconds rather than hours with clearer images. Damadian, along with Larry Minkoff and Michael Goldsmith performed the first MRI body scan of a human being on July 3, 1977. During the 1970s John Mallard built the first full-body MRI scanner at the University of Aberdeen and in 1980 used this machine to obtain the first clinically relevant image of a patient's internal tissues. In recognition of the fundamental importance and applicability of MRI in medicine, Paul Lauterbur and Sir Peter Mansfield were awarded the 2003 Nobel Prize in Physiology or Medicine. Today, MRI scanning is a standard procedure in nearly all fields of RMDs ranging from cartilage and

meniscus assessment in the knee to the sacroiliac joints and to the sensitive assessment of structural damage using a scoring system (RAMRIS)[34].

Of note, a further important and safe imaging procedure employed by rheumatologists is **ultrasonography (US)**[35]. In 1941, the Austrian neurologist Karl Theo Dussik was the first to use ultrasound to image the human body demonstrating the ventricles of a human brain. Subsequently in Glasgow, Ian Donald performed the first diagnostic applications of this technique in an obstetric context. Arthrosonograpy was first used in the early and mid-1970s to detect Baker´s cysts[36]. A major breakthrough was the utilization of ultrasound to detect alteration in the new-born's hips by Graf in 1981[37]. In the 1980s, numerous standardized techniques were described to establish this imaging modality in all fields of orthopaedics, trauma surgery and rheumatology. Newer US techniques included color and power Doppler imaging, which provide color maps of tissues reflecting soft tissue vascularisation and hence inflammation (i.e. synovial tissue). EULAR played and is playing a major role in the development of this field around the world, notably with publishing the first guidelines for musculoskeletal ultrasound in rheumatology in 2001[38].

Finally, after early descriptions by Maricq about the utility of nailfold capillaroscopy in grading the severity of systemic sclerosis, this microscopic analysis of the microcirculation became a validated qualitative and quantitative method since the 90s for the early diagnosis of systemic sclerosis and prediction of clinical complications and optimized management[39]. In 2013, the capillaroscopic analysis was introduced in the new ACR/EULAR guidelines for the classification of SSc brining significant improvement in sensitivity and specificity of the criteria[40].

A timeline of diagnostic development in rheumatology is presented in Figure 2.

Future developments in rheumatology

So – what does the future hold? Medical science is advancing at an unprecedented pace capitalising on remarkable developments in techniques with which to interrogate pathogenesis, phenotype, disease progression and co-morbid impact. Thus molecular methodologies can dissect the genome, epigenome, transcriptome, metabolome and proteome with ever greater clarity. The computational sciences are evident in all elements of practice and will increasingly be so. We will move increasingly to a system based discovery approach whereby 'big data' will dominate as well *in silico* modelling of the pathways and diagnostics with most merit for clinical application. This will in turn inform new insights to the pathogenesis and ultimately the causes of the RMDs. Thus, the future will progressively move RMD treatment earlier in disease progression. Focus will realign on refractory disease states as these become the new "chronic illnesses" in our discipline as acute interventions that are effective prophylactics, or preventions emerge. RMDs may be rationalised at the molecular level and classified according to molecular pathotype rather than only on clinical phenotype. The role of microbiota in RMDs should be an example[41]. Thus RMDs will embrace the developing revolution in precision medicine – now well advanced in cancer therapeutics but only nascent in our field[42]. Taken to logical conclusion this will facilitate the search for prevention and cures of diseases that are currently considered to be chronic and managed only with medications in perpetuity.

Computational science is likely also to influence our daily practice via a revolution in e-Health e.g. with continuous electronic evaluation and downloading of measures of disease activity, prompting semi-automated clinical decision making in real time[43]. Health care systems too will need to evolve to ensure equitable access to therapeutics and advances at manageable cost to patient and payer alike. Partnership between health care professionals,

oversight organisations such as EULAR and governments will need to be agile and responsive to the changing needs of an ageing population that is ever more demanding of robust and positive health related outcomes. Patients already are, but will increase their role as a crucial part to the decision making process both at the individual level and also in terms of policy design and implementation. EULAR is supporting educational projects in this direction.

Concluding section

Midst progress and change mentioned above, it remains vital that organisations such as EULAR provide intellectual and philosophical cohesion and insist that the rights and well-being of people with RMDs remain at the centre of our ambitions. The possibilities for remarkable progress also carry the risk of misdirection and political minimisation of the true impact of RMDs on the lives of our patients. An algorithmic approach to treatment should not be allowed to replace the fundamental depth and care that is implicit in the relationship between health professionals and people with RMDs and that pervades our discipline. Such a caring art of rheumatology should remain our legacy to future generations.

References

1. Barnes C. G. The history of EULAR. EULAR Kilchberg, Switzerland (2007).
2. Strehl C. et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from a EULAR task force. *Ann. Rheum. Dis.* **75**, 952-957 (2016).
3. Svartz N. Salazopyrin, a new sulphanilamide preparation. *Acta Med. Scand.* **110**: 577-598 (1942).
4. Weinblatt M. E. et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N. *Engl. J Med.* **312**, 818-822 (1985)
5. Bakker M. F. et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med.* **156**, 329-339 (2012)
6. Smolen J. et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann. Rheum. Dis.* 2017 Mar 6. pii: annrheumdis-2016-210715. doi: 10.1136/annrheumdis-2016-210715. [Epub ahead of print] (2016)
7. Johnsen A. K. & Weinblatt M. E. Methotrexate. In: Hochberg M. C. et al. (ed.), *Rheumatology*. Elsevier 2011, pp. 509-517.
8. Grigor C. et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet*. **364**, 263-269 (2004)
9. Maini R. et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant

methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet*. **354**, 1932-1939 (1999).

10. Siebert S. et al. Cytokines as therapeutic targets in rheumatoid arthritis and other inflammatory diseases. *Pharmacol. Rev*. **67**, 280-309 (2015).
11. EvaluatePharma® World Preview 2015, Outlook to 2020 8th Edition – June 2015, http://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf, accessed March 2017.
12. Bijlsma J. W. J. et al. Early rheumatoid arthritis treated with tocilicumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. **Lancet**. **388**, 343-355
13. Daigle M. E. et al. The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. *Best Pract Res Clin Rheumatol.* **26**, 649-58 (2012).
14. Van der Woude J. A. et al. Knee Joint Distraction Compared to Total Knee Arthroplasty for Treatment of End Stage Osteoarthritis: Simulating Long-Term Outcomes and Cost-Effectiveness. *PLoS One*. May 12;11(5):e0155524 (2016)
15. Ruiz M., Cosenza S., Maumus M., Jorgensen C. & Noël D. Therapeutic application of mesenchymal stem cells in osteoarthritis. *Expert Opinion on Biological Therapy*. **16**, 33-42 (2016)
16. Brady J. Jubilee lecture at ARHP congress, San Francisco (2015).
17. Kouloumas M., Vice President PARE, EULAR. Personal communication, January 2017
18. Dörner T., Egerer K., Feist E. & Burmester G. R. Rheumatoid factor revisited. Curr. Opin. Rheumatol. **16**, 246-253 (2004).

19. Puszczewicz M. & Iwaszkiewicz C. Role of anti-citrullinated protein antibodies in diagnosis and prognosis of rheumatoid arthritis. *Arch. Med. Sci* **7**, 189-194 (2011).
20. Aletaha D. et al. Rheumatoid Arthritis Classification Criteria. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Ann. Rheum. Dis.* **69**, 1580-1588 (2010).
21. Shi J. et al. Carbamylation and antibodies against carbamylated proteins in autoimmunity and other pathologies. *Autoimmun. Rev.* **13**, 225-230 (2014).
22. Ospelt C. et al. Carbamylation of vimentin is inducible by smoking and represents an independent autoantigen in rheumatoid arthritis. *Ann Rheum Dis.* 2017 Feb 9. pii: annrheumdis-2016-210059. doi: 10.1136/annrheumdis-2016-210059. Epub ahead of print. (2017).
23. Hargraves M. M., Richmond H. & Morton R. J. Presentation of two bone marrow elements: The ‘tart’ cell and the ‘L.E.’ cell. Proc. Mayo Clin. **23**, 25–28 (1948).
24. Miescher P. & Fouconnet M. L’absorption du facteur ‘LE’ par des noyaux cellulaires isolés. *Experimentia* **10**, 252–254 (1945).
25. Hiepe F., Dörner T. & Burmester G. R. Editorial Overview: Antinuclear Antibody- and Extractable Nuclear Antigen-Related Diseases. *Int. Arch. Allergy Immunol.* **123**, 5–9 (2000).
26. van der Woude FJ et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet*. **8426**, 425-429 (1985).
27. Haase A., Landwehr G. & Umbach E. (eds.). Röntgen Centennial: X-rays in Natural and Life Sciences, Singapur: World Scientific, S. 7–8 ISBN: 981-02-3085-0 (1997).
28. Larsen A., Dale K. & Eek M. Radiographic Evaluation of Rheumatoid Arthritis. *Acta Radiologica Diagnosis*. **18**, 481-91 (1977)

29. Sharp J. T. et al. Reproducibility of Multiple-observer Scoring of Radiologic Abnormalities in the Hands and Wrists of Patients with Rheumatoid Arthritis. *Arthritis Rheum.* **27**, 61-4 (1985)
30. van der Heijde D. M., van Riel P. L., Nuver-Zuwart H. H., Gribnau F. W. & van de Putte L. B. Effects of hydroxochloroquin and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet*, **1846**, 1036-1038 (1989).
31. Mishra S. K. and Singh P. History of Neuroimaging: The Legacy of William Oldendorf. *Journal of Child Neurology*, **25**, 508-517 (2010).
32. Rubin G. D. Computed Tomography: Revolutionizing the Practice of Medicine for 40 Years. *Radiology*. **273**, S45-S74 (2014).
33. A quick history of the MRI in two views - words and pictures - http://www.twoviews.com/mri-imaging/history.html#sthash.LPFKbwrI.dpbs, accessed 11 March 2017.
34. Lassere M. et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 3: an international multicenter reliability study using the RA-MRI Score. *J. Rheumatol*. **30**, 1366-1375 (2003).
35. Woo J. A short History of the development of Ultrasound in Obstetrics and Gynecology. http://www.ob-ultrasound.net/history1.html, accessed 11 March 2017
36. Gompelt B. M. & Darlington L. G. Grey scale ultrasonography and evaluation of popliteal cyst. *Clin. Radiol*. **30**, 539-545 (1979).
37. Graf R. The diagnosis of congenital hip-joint dislocation by the ultrasonic Combound treatment. *Arch. Orthop. Trauma Surg*. **97**, 117-133 (1980).
38. Backhaus M. et al. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann. Rheum. Dis.* **60**, 641–649 (2001).

39. Maricq H. R. & LeRoy E. C. Patterns of finger capillary abnormalities in connective tissue disease by ‘widefield’ microscopy *Arthritis Rheum.* **16**, 619–628 (1973).
40. Cutolo M., Sulli A. & Smith V. Assessing microvascular changes in systemic sclerosis diagnosis and management. *Nat Rev Rheumatol.* **6**, 578-587 (2010).
41. Abdollahi-Roodsaz S., Abramson S. B. & Scher J. U. The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions. *Nat. Rev. Rheumatol.* **12**, 446-455 (2016).
42. van der Vlist M., Kuball J., Radstake T. R. & Meyaard L. Immune checkpoints and rheumatic diseases: what can cancer immunotherapy teach us? *Nat. Rev. Rheumatol.* **12**, 593-604 (2016).
43. Topol E. Digital medicine: empowering both patients and clinicians. *Lancet* **388**, 740-741. (2016).