

Twenty women of XX century: major contributions and key discoveries in rheumatology.

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Abstract

In the XX century rheumatology has seen an exponential growth. Discoveries in the pathophysiology of rheumatic diseases, progress in research methodology and novel treatments cardinally changed the natural course of rheumatic diseases and revolutionized patient management. Although underrepresented in this field, women have made considerable input in advancing our specialty towards the new era. In this article we acknowledge key scientific discoveries and major contributions made by 20 brilliant women scientists that shaped the field of rheumatology in the XX century. We hope that achievements of these remarkable women will inspire young rheumatologists and researchers.

Manuscript

In the last 100 years our relatively young specialty has seen an exponential growth. Key discoveries in understanding pathophysiology, diagnostic and therapeutic advances changed the image of a wheel-chair bound patient with advanced joint deformities we see in old rheumatology books. Originally a predominantly male specialty, in the last decades rheumatology has seen a shift of balance. Although, women are still underrepresented and occupy significantly fewer senior academic positions¹ and senior authorship positions² than their male counterparts, major efforts have been made towards gender equality and equity. Some of the key discoveries in rheumatology have been made by women. In this article we acknowledge major contributions made by 20 of these groundbreaking women scientists that shaped the field of rheumatology as we know it today. This list is of course subjective and we were not able to encompass all notable women that contributed to our specialty.

One of the first prominent women in the history of rheumatology was the Swedish physician Nanna Svartz. She worked in Karolinska Institutet in Stockholm and was the first woman to be appointed a full professorship in Sweden in 1937¹. Her research focused on ulcerative colitis, rheumatoid arthritis and, interestingly, intestinal flora. She described microscopic similarities between the two diseases and suggested infectious origin of the arthritis. Later on, she had the idea to combine anti-inflammatory properties of acetylsalicylic acid with antibacterial properties of sulfonamide, thus developing salazopyrine, the first anti-rheumatic drug, used until this day^{3,4}.

It is difficult not to mention Brigitte Askonas who has made major contributions in understanding the functioning of the immune system. Born in Vienna in 1923 and immigrated to Canada at young age, she studied biochemistry in Montreal and later on defended her PhD in the University of Cambridge⁵. In the 60s, she first described the assembly of immunoglobulins from heavy and light chains⁶ and documented the production of antibodies by a variety of organs other than lymphoid tissues⁷. Slowly unraveling the immune system like a ball of yarn, she discovered the role of macrophages as antigen presenting cells, described antigenic specificity of the T-cells and studied the structure of the T-cell receptors⁸.

In more that hundred years only 12 women were awarded the Nobel prize in medicine and physiology. Gertrude B. Elion was one of them. She was born in 1918 in New York from Lithuanian and Russian parentage⁹. She was a biochemist and studied the synthesis of nucleic acids in the 40s. The understanding of these synthesis pathways led to a discovery of 6-mercaptopurine and revolutionized the way drugs were developed. From a trial and error approach commonly used in those times, Elion moved to a scientific approach based on the understanding of the underlying mechanisms¹⁰. She discovered, among others, azathioprine and allopurinol, drugs that truly changed management of patients with rheumatic diseases.

Marian Wilkins Ropes was one of the pioneers in American medicine and first woman to be elected the president of the American Rheumatism Association. Until 1936 women were not accepted to Harvard Medical school, therefore she studied medicine in John Hopkins. In 1932 Dr Ropes returned to Massachusetts General Hospital and became first woman to be appointed as a resident in medicine and later on first woman as assistant professor of

clinical medicine.¹¹ Through her long and productive career she studied composition and function of synovial fluid and its changes in different rheumatic diseases. Later on, her research focused on systemic lupus and she was one of the first to describe the increased risk of infection in SLE patients¹². Not only did she make major contributions in understanding rheumatic diseases but she also laid groundwork for possibility of medical career for women in medicine and in rheumatology.

Valentina Nasonova was born in Dnepro, Ukraine and was a prominent Soviet rheumatologist and member of Russian Academy of Sciences. With the advantage of equal rights in the USSR era, she finished medical studies in 1946 and pursued an academic career in The Institute of Rheumatology in Moscow where she held the position of the director of the Institute for more than 30 years (1970-2001)¹³. Although veiled by the iron curtain, she completed extensive clinical research in systemic diseases and SLE in particular, describing the nature of different anti-DNA antibodies¹⁴. Hardworking, meticulous and inquisitive, she has inspired several generations of rheumatologists. Up until 2021, she had been the only female president of EULAR in their more than 70 years history¹⁵.

Barbra Ansell was one of the pioneers in the field of pediatric rheumatology. In her MD thesis (1965) she developed classification criteria for juvenile idiopathic arthritis (JIA)¹⁶. Ansell dedicated her lifelong career to studying rheumatic diseases in children. She conducted numerous clinical trials to search for new efficient treatments in JIA in the pre-biological era^{17,18} and was a strong advocate of multidisciplinary management. She described association of antinuclear antibodies and uveitis in children with JIA¹⁹ and characterized CINCA (Chronic Infantile Neurological Cutaneous and Articular)

syndrome as an entity²⁰. Throughout her career Professor Ansell supported women in building their careers and strove to facilitate their dual role as specialists in training and mothers¹⁶.

Another notable rheumatologist, Renate E. Gay, studied medicine in Leipzig and further perused her studies in the University of München where she passed the state exam in 1974 and was promoted in 1975²¹. She pursued an academic career at the University of Birmingham, Alabama. Professor Gay extensively studied different types collagen in skin, joints²² and its role in pathophysiology of rheumatic diseases, systemic sclerosis in particular. In 1984 she was the first woman to be awarded the prestigious Carol Nachman Prize for outstanding contributions in research in rheumatology. Professor Gay further studied function of synovial fibroblasts, role of Toll-like receptors^{23,24} and made substantial contributions in understanding pathophysiology of RA.

After graduating magna cum laude from New York University, Jane E. Salmon earned a medical degree in 1978 from Columbia University²⁵. She was the first woman to be enrolled in their Medical Scientist Training Program. Professor Salmon elucidated the mechanisms of premature cardiovascular disease in systemic lupus. She studied complement activation and pregnancy outcomes in SLE²⁶ and anti-phospholipid syndrome (APS)²⁷ and demonstrated the higher risk of an early-onset pre-eclampsia in women with SLE²⁸. Her research deepened the understanding of the complex hormone-immune mechanisms linked to pregnancy loss²⁹. She is the director of the Lupus and APS Center of Excellence at Hospital for Special Surgery. Her research was pivotal in understanding pathophysiology of SLE, APS and their link with the pregnancy.

Bevra Hahn received her MD and trained in rheumatology at John Hopkins University School of Medicine. For 30 years she was the chief of the Rheumatology department at University of California, Los Angeles. Her fascinating research helped to understand the complexity of T and B cell interactions and the role of T-cells in pathogenic antibody production in systemic lupus^{30,31}. Interestingly, she studied immune tolerance in SLE, developing a peptide able to suppress auto-reactive T cells in models of lupus nephritis³² and studied the mechanisms of accelerated atherosclerosis in SLE³³. For these works she received the Carol Nachman prize, awards from the British and Dutch Society for Rheumatology and the Gold Medal of the American College of Rheumatology (ACR).

Dafna D. Gladman, is Professor of Medicine at the University of Toronto, and devoted her life to clinical and translational research, focusing on psoriatic arthritis (PsA) and SLE³⁴.

Among many merits, Professor Gladman established the SLICC (Systemic Lupus International Collaborating Clinics) in 1987. This group developed a damage index for lupus and validated activity measures, allowing for the standardized assessment of SLE³⁵. In 1978 she established a prospective PsA cohort helping to understand comorbidities and radiographic damage in the disease^{36,37}. Among many awards, professor Gladman received the Mentor of the Year Award from the Royal College of Physicians and Surgeons of Canada and was the recipient of the Verna Wright Prize for outstanding contributions to the field of Psoriatic Arthritis.

Johanne Martel-Pelletier dedicated her career to research in the field of osteoarthritis (OA). She earned her Master's and PhD degrees in Physiology from the University of Montreal

(1975 and 1975 respectively) and completed her training in rheumatology in the University of Miami in 1981. Together with Professor J-P Pelletier she has made substantial contributions in understanding mechanisms of cartilage destruction and repair. Professor Martel-Pelletier described role of different pro-inflammatory cytokines and metalloproteinases in OA^{38,39} and identified potential therapeutic targets for preventing cartilage damage⁴⁰. She has been awarded a number of fellowships and awards including the Carol Nachman Prize, King Faizal Prize for Medicine and ILAR Rheumatology Prize.

In the field of SLE, recognition should also be given to Mary Crow⁴¹. She is Professor in the Division of Rheumatology at Weill Cornell Medical College and director of the Autoimmunity and Inflammation Research Program at the HSS Research Institute. Her academic career focused on unraveling the cellular and molecular mechanisms that underlie SLE; one of her most important contributions was the identification of the crucial role of interferon-alpha in the pathogenesis of the disease, the immunologic consequences of its chronic activation in SLE patients⁴², and the possibility of utilizing this as a therapeutic target⁴³. She has received numerous awards including the Presidential Gold Medal of the American College of Rheumatology in 2018.

Acknowledgement should be given to Monica Østensen who dedicated her career to studying women's reproductive health and the relationship between pregnancy and rheumatic diseases. Professor Østensen works at the National Advisory Unit on Pregnancy and Rheumatic diseases, Norway. Throughout her long academic career she studied pregnancy outcomes in patients affected by different rheumatic diseases (SLE, Sjogren Syndrome, RA, SPA), safety and toxicity of the treatments and their impact on fertility and pregnancy⁴⁴. She

gave a major contribution to understanding the function of humoral immunity during pregnancy in patients with rheumatic diseases⁴⁵ and the understanding the impact of pregnancy on RA activity⁴⁶.

The name of Désirée van der Heijde is probably known to every rheumatologist. She obtained a medical degree at the Catholic University in Nijmegen, the Netherlands in 1986. In her thesis she developed and validated the DAS (Disease Activity Score) that allowed standardized assessment of RA patients. In her doctoral work she also developed a modification of the Sharp radiographic score, that became a golden standard in assessment of radiographic progression in rheumatoid arthritis⁴⁷. Her extensive methodological work in radiographic evaluation of RA, psoriatic arthritis (PsA) and axial spondyloarthritis (axSPA) fundamentally changed the design of clinical trials in favor of a standardized and systematic approach⁴⁸.

After receiving her medical and academic degrees in Hungary, Katalin Mikecz perused research in Montreal and then at Rush University in Chicago. Together with Edit Buzás, she studied proteoglycan-induced arthritis in animal models and provided a substantial contribution to understanding mechanisms of immune activation in early stages of RA⁴⁹. She investigated role of adhesion molecules (CD44, CD2L) in leucocyte homing and development of autoimmunity, underlining the importance of innate immune system in progression of arthritis⁵⁰. Moreover, she recently explored how the overexpression of the Src homology region 2 domain-containing phosphatase-1 (SHP-1) gene impact on the arthritis susceptibility, identifying a new possible future therapeutic target in RA⁵¹. Therefore, she shed light on immune mechanisms of early RA. In 1995 for outstanding contributions in the

field of rheumatology, together with Professor Buzás she was awarded the prestigious Carol Nachman Prize.

Cornelia Weyand finished her training in medicine and immunology in Germany and pursued further training in rheumatology at Stanford University. In more than 40 years of a fruitful scientific career, she and her team studied mechanisms of inflammation and tissue damage in large vessel vasculitis. She demonstrated that Th1 cells are unaffected by glucocorticoid therapy and are responsible for maintaining chronic inflammation in GCA⁵². Further, Professor Weyand investigated mechanisms of premature T cell senescence in RA. In more recent research in immunometabolomics she demonstrated that in RA mitochondrial disbalance promotes differentiation of CD4+ T cells into effector cells and that intermediate metabolites of Krebs cycle play important role as regulators of T cell function⁵³. Professor Weyand has received numerous awards and honors, including Carol Nachman prize in 1995.

Seza Ozen graduated (1982), completed her residency and doctoral research at Hacettepe University in Ankara, Turkey. After post-doctoral fellowship at Stanford University, California, she returned to Hacettepe University in 1992 where she is currently a professor and head of the Department of Pediatric Rheumatology⁵⁴. She is a world renowned expert in auto-inflammatory diseases, Behçet's disease in particular, and paediatric vasculitis. Professor Ozen has done extensive research on genetic and clinical aspects of Familial Mediterranean Fever and was a member of the EULAR committee, developing management recommendations⁵⁵. She has also been a member

of the European committee that published recommendations for childhood vasculitides⁵⁶.

In Japan, women physicians hold on average 4.1% of faculty positions². Yuko Kaneko is an associate professor at the Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan⁵⁷. She has made a significant contribution to the understanding of pathophysiology of IgG4-related disease (IgG4-RD). She showed the importance of IL-4 in its pathogenesis, in particular that IL-4 producing T-helper cells contribute to plasmablast differentiation and IgG4 class switching in this disease^{58,59,60}. Together with her team, Professor Kaneko has demonstrated that IgG4-lymphadenopathy is associated with a higher disease activity and identified eotaxin-3 as a potential new biomarker of IgG4-RD⁶¹. She also extensively studied the IL-6 pathway and effects of IL-6 inhibition in RA and Still's disease^{62,63,64}.

Ellen M. Gravallese is Chief of the Division of Rheumatology at Brigham and Women's Hospital and Professor of Medicine at Harvard Medical School⁶⁵. She is an internationally recognized expert in osteoimmunology and has extensively studied mechanisms of bone remodeling in inflammatory joint diseases⁶⁶, the link between inflammation and joint destruction^{67,68} and identifying potential therapeutic targets⁶⁹. Dr Gravallese served as the 83rd President of the ACR (2019-2020) and is the recipient of numerous awards including the Steven Krane Award from the American Society for Bone and Mineral Research (2017) and the Carol Nachman Prize (2019).

Professor Eloisa Bonfá is the Physician-in-Chief of the Rheumatology Division of the University of São Paulo, the largest tertiary referral center for autoimmune rheumatic disorders of Latin America⁷⁰. She graduated from the University of São Paulo Medical School in 1981, completing training in rheumatology and her PhD in the same University. Professor Bonfá's main area of research is SLE, in particular, she studied the role of specific antibodies in pathogenesis of the disease, showing the association between anti-ribosomal P antibodies and neuro-psychiatric SLE^{71,72} and the arrhythmogenic potential of purified Ro/SSA antibodies⁷³. More recently, she has described the association of anti-ribosomal P antibodies and lupus membranous glomerulonephritis ⁷⁴.

Together, these researchers have made important contributions to the understanding of pathophysiology of rheumatic diseases and contributed to progress in our specialty. We hope that the achievements of these remarkable women will inspire young rheumatologists and researchers, and would like to conclude with the words of Professor Bevra Hahn: "We should do what we can do in the 24 hours allotted to each day. Be satisfied with achievements, grieve briefly over defeats. Move ahead" ⁷⁵.

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