


Review Article

Out of the Trenches: A Review of Modern Rheumatology's Relationship with War

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Abstract

This paper provides a brief review of how wars in recent history have shaped the development of rheumatology as a medical specialty. This history is not widely known in the medical field and appears to have been forgotten. However, it is important to the field of both military medicine and rheumatology in a civilian context. Many rheumatic diseases were recognised for the first time as a result of doctors treating arthritis in soldiers during World War I and World War II. Chemical Weapons in both wars lead to the discovery of many Disease Modifying Anti Rheumatic Drugs still commonly used today in rheumatology. During World War I, 93,000 cases of arthritis were reported in US troops. Ten years after the end of World War I in the US, the government was paying \$10,000,000 a year to around 35,000 ex-service personnel for disabilities as a result of chronic arthritis, demonstrating arthritis in military history is significant.

Keywords: Arthritis; Military rheumatology; Rheumatism; Rheumatology history; War medicine

Introduction

Surgery's relationship with war is well recognised. This is particularly true of orthopaedic and trauma surgery. However, the same cannot be said for rheumatology; a medical specialty that has come to be associated with slow, deep intellectual and academic endeavour and not the fast-paced chaotic nature of emergent medical presentations of the battlefield.

However, an examination of the history leads one to draw a very different conclusion about rheumatology's relationship with military medicine. From the development of immunosuppressive agents derived from mustard gas used as chemical weapons during World War I (WWI) to the discovery of cortisone following events in World War II (WWII), to the recognition that 'rheumatism' had a multitude of causes, modern rheumatology has a long and close association with war. Several rheumatic diseases have been documented for the first time in literature by doctors treating soldiers engaged in active duty. This paper will review the origins of modern Western rheumatology and articulate its close connection with warfare and military activities.

Rheumatology was a field well documented in the ancient world by various systems of medicine, including those of India, China and Ancient Greece. The origin of the word rheum is related to the middle English word reume "watery fluid" and from Greek and Latin words rheuma "to flow" all of which are related to the Proto-Indo-European root sreu to flow [1]. This is possibly with reference to the clinical phenomenon of synovitis commonly encountered in rheumatic diseases. Charles Richet, the physician who first

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described anaphylaxis, wrote a paper at the end of the 1900s [2] where he questions the usefulness of the theory of four humours, which was the prevailing system of medicine and pathophysiology throughout Europe for several centuries until that point. He asks if any doctors had seen the humor phlegm that was thought to result in rheumatism, proposing the four humours were theoretical rather than having any physical basis in the body itself.

Ancient knowledge systems including those of the four humours persisted in Old-World rheumatology practice until major wars of the last 300 years gave birth to the modern era of rheumatology, with advancements in the understanding of autoimmunity and autoinflammation rapidly advancing after the end of WWII.

Prior to WWI and WWII, only a few causes of 'rheumatism' were known with ill-defined disease entities and imprecise use of terminology. Terms such as chronic arthritis, rheumatoid arthritis, and rheumatic fever were not well differentiated entities as they are today and many terms such as 'acute rheumatism' were indiscriminately used to describe most cases of acute arthritic presentations. Terms such as myositis, sacroiliac deformity, and lumbago were subjective. In part this was due to a lack of understanding of the immunologic phenomena and pathophysiologic pathways that only developed in the post-war period from the 1940s onwards.

It is recognised that war has influenced the language of immunology and therefore rheumatology. Historically, immunology literature has commonly involved militaristic metaphors, for example in the late 1800s white blood cells were described as 'sentinels waging a war on potential invaders' [3]. Some writers, including Turney [4], suggest medical research, so closely linked with the Second World War, cemented the use of military terms in immunology-related literature. In recent times it has been suggested that a militaristic viewpoint of the immune system is potentially inaccurate and should be abandoned [4].

Prevalence of Rheumatic Diseases in Military Personnel and Economic Burden of Disease

Historical records from WWI reveal that out of the 10 most common medical presentations, two of these were directly rheumatic in nature, namely inflammation of connective tissue, and rheumatism [5].

The First World War resulted in the death of over 9 million soldiers and between 7–10 million civilian deaths [6,7]. Famous rheumatologists Hench and Boland in their 1946 paper [8] reported that around 93,000 cases of rheumatism were recorded by soldiers during WWI. This had an incidence rate of 22.4 per 1000 soldiers according to Hench and Boland [8] and 22.7 per 1000 according to US government records [9]. Four common rheumatic diseases accounted for 80% of

the cases, those being rheumatoid arthritis, rheumatic fever, osteoarthritis, and muscular rheumatism [8].

Hench and Boland [8] report that in 1931, ten years after the end of WWI in the US, the government was paying \$10,000,000 a year to around 35 000 ex-service personnel for disabilities as a result of chronic arthritis.

As a result of data collected from WWI and the recognition that rheumatic diseases following active service posed a serious economic and health burden to the US government, during WWII the US Surgeon General in consultation with the American Rheumatism Association established specialised rheumatology units should the need for similar numbers of rheumatologic presentations eventuate. By 1946 when Hench and Boland wrote their paper 5 such centres were established; 3 for acute rheumatic fever and 2 for chronic rheumatologic presentations [8].

In 1943 the establishment of a Rheumatism Centre at the Army and Naval Hospital had taken place. The location was next to natural hot springs at Hot Springs in Arkansas, the use of which was thought to aid patients suffering from 'rheumatism'. Informally the centre had been a medical pilgrimage centre since the early 1880s for military personnel suffering from rheumatic diseases [8,9].

In line with this preparation, government-commissioned building works for the Army and Navy General Hospital commenced in 1941 and were completed in 1943, at a cost of around \$1,500,000 [9]. The main building was six-floors with a bed capacity of 518 [9]. By 1944 the centre was seeing an average of 700 rheumatology patients a day. By 1945 the centre had seen 5315 patients over the previous 18 months [8]. The most common presentations included rheumatoid arthritis, spondylitis, 'psychogenic rheumatism', osteoarthritis, rheumatic fever, gonorrhoeal arthritis, and miscellaneous and unclassified rheumatic diseases [8]. WWII saw rheumatic presentations at an incidence rate of 20.7 per 1000 soldiers according to Hench and Boland [8].

Hospitals in other locales including those in the Mediterranean and the Western Pacific Base Command of the Central and South Pacific Theatre also reported rheumatic presentations with relative frequency [9].

In 1945 Glover published a paper titled 'Acute Rheumatism in Military History' [10]. He referred to rheumatic fever in this title stating 'acute rheumatism influences war and preparation for war in five main ways:

- 1) Causing medical casualties in the field requiring prolonged treatment;
- 2) Causing post-tonsillitis barrack epidemics that disrupt training;
- 3) The long-term sequelae of rheumatic fever results in expensive pension claims for the government;

- 4) Rheumatic fever causes organic heart disease in children reducing the pool of potential military recruits in the civilian population; and
- 5) Acute rheumatism might be the precursor of chronic diseases such as fibrositis, lumbago, and sciatica'

Glover [10] claimed that acute rheumatism affected the course of war throughout history by claiming more lives than death on the battlefield itself. Whilst this statement is likely an exaggeration, it demonstrates how seriously rheumatism was taken by physicians at the time the paper was written and demonstrates the connection between rheumatism and war.

Glover notes the earliest statistics relating to rheumatism in Western military history can be attributed to John Pringle who fought in the Pragmatic Army during the Battle of Dettingen and in 1743 describing that following an attack based in Brussels resulting in his deployment to Germany, there was an influenza epidemic that broke out. This resulted in soldiers presenting with rheumatic pains, some also with fevers. Of the army of 14,500 men, there were 51 such presentations representing an incidence rate of 3.5 per 1000 soldiers.

Incidence of rheumatic disease of several wars is provided by Glover in a number of other conflicts from the Crimean war in 1854 with an incidence rate of 24.5 per 1000 troops, to the American Civil War which held the highest incidence rates of any of the conflicts he studied at 65.3 per 1000 for the Union Army and 90 per 1000 soldiers for the Confederates. The South Africa War of 1899-1902 saw 44 per 1000 troops and in 1915 the Dardanelles experienced a rate of 56 per 1000. Other conflicts he researched had significantly lower incidence rates.

Glover [10] asked the interesting question, 'Why was there more rheumatism in the high and healthy climate of South Africa than in the mud of the trenches of 1915?', but then attributes the vast number of rheumatology presentations in South Africa to ration shortages, long marching distances, and fierce weather conditions, which rather contradicts his statement of South Africa having a healthy climate. Until the mid-1900s, rheumatic disease was thought to be greatly influenced by weather conditions resulting in health advice to seek retreats in warm climates, balneotherapy, and hot spring therapy.

Military records from many armed conflicts including WWI and WWII, the American Civil War, and even more recent wars such as the Gulf War, reveal that rheumatic diseases amongst those serving were a common presentation [9].

Hench and Boland [8] write that for an army of a size of 800,000 soldiers, an average of around 5400 cases of acute rheumatism could be expected a month totalling around

180,000 cases of rheumatic presentations in under a three-year period. About 64,000 of these cases would go on to develop chronic arthritis.

Smith [9] estimates the total number of rheumatic disease cases in US troops to be between 530,000 and 573,000 during the course of WWII.

Disqualification from service as a result of rheumatic conditions remained an issue during both WWI and WWII. During WWI the disqualification rate was 5.9 per 1000 soldiers compared to 7.2 per 1000 soldiers in WWII [9]. According to sources rates varied as a result of increased age of fighting troops in WWII as well as improved diagnostic techniques [9]. During the Second World War discharges due to rheumatic disease totalled 64,619 enlisted personnel [9].

Rheumatic Fever, Reactive Arthritis (ReA) and Seronegative Spondyloarthropathies (SpA)

The diagnostic criteria for many rheumatic diseases were developed, or refined as a result of activities during WWII including the recognition of "rheumatoid spondylitis" which paved the way for the recognition of the seronegative spondyloarthritides [11]. As recorded by the physician and rheumatologist James Glover [10], reactive arthritis was first described in connection with military activity with several prominent physicians documenting it throughout history. He reports physician Sydenham had described gonorrheal rheumatism which accounted for a large proportion of rheumatic presentations in military troops prior to 1860.

In 1818, English physiologist and surgeon Sir Benjamin Brodie [12] wrote a book that described reactive arthritis very clearly. He documented many cases of bone and joint diseases throughout his career. Cooper in 1840 reported a case of gonococcal arthritis in the *Lancet*. Nazi war criminal and physician Hans Reiter who served in both WWI and WWII in 1916 documented a case of a German soldier who developed a triad of arthritis, conjunctivitis, and non-gonococcal urethritis. However, in the same year, 1916, two French clinicians, Noel Fiessinger, and Emile Leroy described an 'oculo-urethral-synovial' syndrome that developed post-dysentery in some patients [13,14]. Despite this, Reiter's name only became synonymous with this post-infectious triad of symptoms.

In each of the conflicts researched by Glover [10], the causative infectious agents resulting in both acute and chronic reactive arthritis were likely to have been varied. Due to populated conditions, human movement, endemic infections in certain countries occupied by troops as well as often squalid conditions and poor sanitation associated with the battlefield, infectious disease outbreaks often go hand in hand with military activities giving rise to scenarios where large numbers of cases of ReA could occur. As such, widespread

conflict and movement of troops has the capacity to spread pandemics as in the case of the infamous H1N1 Spanish flu outbreak of WWI [15]. These factors inevitably result in a variety of rheumatic diseases secondary to infectious diseases ranging from viral and bacterial arthralgias such as those reported in WWI trench warfare including:

- Trench fever associated myalgia and arthralgia (caused by lice carrying the bacteria *Bartonella quintana*) Of note modern 'urban trench fever' is associated with homelessness, immunocompromised, and socio-economically challenged populations [15].
- Septic arthritis from tuberculosis, disseminated gonococcal and syphilitic infections, staphylococcus aureus and associated poor sanitation were relatively common [15].
- ReA likely enteropathic in nature as well as Sexually Acquired Reactive Arthritis (SARA) which could be caused by a wide variety of infectious agents ranging from malaria, gonorrhoea, syphilis, dysentery, and various viruses encountered by troops.

In 1946 Boland and Shebesta [16] published a paper recognising a condition they described as rheumatoid spondylitis, which later became known as Ankylosing Spondylitis (AS). They noted the radiographic features of the disease, but concluded most presentations were early on in the disease process and therefore did not demonstrate classic features of 'bamboo spine'. They estimated 1,084 instances of AS were diagnosed during a 22 month period, or 18.1% of the 6,000 consecutive admissions seen during that period.

More than 160,000 cases of "acute rheumatism" were reported amongst the soldiers of the American Civil War [14]. Rheumatic Fever was attributed as the cause. Other infectious arthropathies were also common, however, the mechanism was not understood at the time. Over 246,000 cases of "chronic rheumatism" were reported [14].

Reactive arthritis following dysentery was a major cause of rheumatic disease in the American Civil War. A remarkable 12,000 soldiers were discharged due to chronic rheumatism [14]. This included the diagnosis of "lumbago," which possibly represented axial spondyloarthropathy as well as non-specific lower back pain.

More than 2 million cases of diarrhoeal illnesses and 100,000 cases of urethritis were reported from the American Civil War with estimates that there may have been as many as 30,000 cases of reactive arthritis among Union troops [14].

Fibromyalgia

In their 1946 paper, Hench and Boland [8] go on to describe in some detail the phenomena of psychogenic rheumatism and fibrositis. It was Boland who first recognised some

soldiers were suffering from what he coined 'psychogenic rheumatism' and another condition 'primary fibrositis'. Both these crude diagnoses ultimately paved the way for the understanding of what later became known as fibromyalgia [13].

The Complex Regional Pain Syndrome

Battlefields have provided a plethora of case studies through which the understanding of neurologic conditions developed [13]. Some conditions were first recognised during the Civil War by Philadelphia doctor, Silas Weir Mitchell, who published the first case of causalgia now known as Complex Regional Pain Syndrome (CRP) [13].

Post Traumatic Arthritis

A recent paper exploring the increased rates of post-traumatic osteoarthritis in military personnel by Rivera et al. [17] attributes arthritis caused by injuries during battle to a range of causes including falls, fractures from explosions, arthrotomies from explosions, soft tissue injuries from explosions, and gunshot wounds. It could be assumed similar injuries would account for historical cases and also for Military veterans reported as experiencing an increased incidence of arthritis compared with the general population.

Disease Modifying Anti-Rheumatic Drugs and War

Many of the Disease Modifying Anti-Rheumatic Drugs (DMARDs) used today as first-line therapies in rheumatic diseases have their origins with chemical weapons used in WWI, or were developed as a direct result of research emerging out of wartime efforts of WWII.

For example, the development of both methotrexate and cyclophosphamide as a DMARD originates with mustard agents [18]. Doctors Edward and Helen Krumbhaar first began researching its potential medical uses during WWI [19] when it was first used as a chemical weapon by German forces. Its effects were devastating and included ocular irritation, nausea, vomiting, external and internal widespread blistering of epithelial surfaces and earned it the name 'King of the Battle Gases' [20].

Following WWI, experiments and interest in the medical use of chemical warfare agents for purposes other than weapons developed [21]. During WWII American Lieutenant Colonel Stewart Francis Alexander who was an expert in chemical warfare recognised suppression of lymphoid and myeloid tissues in those exposed to mustard gas [22]. This resulted from the accidental spillage of sulfur mustards on military troops following a ship bombing in Italy, during WWII [23]. Subsequent investigations led to researchers such as Winternitz and Faber's discovery that nitrogen mustards could arrest the progress of cancer resulting

in the first chemotherapy agents [20,23]. Collaborative research including by Yellapragada Subbarao, an Indian scientist working in the U.S. [24] lead to the development of methotrexate and the recognition it could be used to successfully treat rheumatoid arthritis. Later methotrexate was approved for use in rheumatology in 1988 [24].

The research on mustard gas led researchers Hitchings and Elion to isolate 6-mercaptopurine in 1951 which subsequently resulted in the development of azathioprine in 1956 by Lang, Hitchings, and Elion, the prodrug from which 6 mercaptopurine is produced. Azathioprine was first approved for medical use in 1968 [25].

Research undertaken around the same time led to the study of cyclophosphamide as an alkylating agent in 1960 by researchers Foye et al. [26]. Cyclophosphamide was first approved for medical use in 1959.

Antimalarial and DMARD hydroxychloroquine was the result of industrialized medications that occurred during the war because malaria was a leading cause of disease among soldiers, especially in troops deployed to the South Pacific [27,28]. The synthetic version of hydroxychloroquine was synthesised in 1955 [27].

In the early 1940s, Mayo Clinic chemist Edward Kendall successfully isolated cortisone and cortisol [28]. On the other side of the world in Europe, Polish chemist Tadeusz Reichstein achieved the same discovery [29]. This research was fuelled by rumours during WWII that Germans were preventing their Luftwaffe pilots from experiencing altitude sickness with a compound extracted from adrenal glands [30]. This led to research by the Allies for a similar compound, however, it was only after the war that the medical significance of cortisone was first truly appreciated. In 1949 American rheumatologist Hench discovered glucocorticoids effectively treated patients with rheumatoid arthritis and was awarded a Nobel prize in Physiology, or Medicine for his efforts along with Kendall and Reichstein in 1950 [31]. The central role of glucocorticoids and their use in the treatment of rheumatic diseases over the next 80 years requires no explanation.

Recent Military and Combat Rheumatology Research

Today rheumatology remains an important medical specialty in relation to combat medicine.

For example, one study of 250 presentations of gulf war veterans, 56% were referred for rheumatology consultation. Of those 14% were diagnosed with rheumatic disease and 59% had soft tissue diagnoses [32].

There is growing recognition in the literature Posttraumatic Stress Disorder (PTSD) (whether it is military, or otherwise) might be linked with the development of a variety of autoimmune disorders [33]. There exists a bidirectional relationship between inflammation and PTSD [34]. One

study from 2020 reported that 40% of US military personnel seeking treatment for PTSD had comorbid fibromyalgia [35]. Studies by Bejarano et al. [36] and Lee et al. [37] observed an increased risk of those suffering from PTSD and the subsequent development of Rheumatoid Arthritis (RA). Although the study by Lee et al. [37] was not on military personnel it looked at large data from over 54,000 nurses and showed that compared to no history of PTSD, or trauma, the hazard ratio of ≥ 4 PTSD symptoms and incident RA was 1.76 (95% CI 1.16,2.67) with the risk of developing RA increasing with an increasing number of PTSD symptoms. Extrapolating this information, it could be assumed PTSD is one of several factors contributing to higher rates of chronic inflammatory arthritis reported in war veterans throughout historical literature.

Ongoing research has demonstrated military service involving dust exposure conferred an increased odds of developing rheumatoid arthritis (odds ratio [OR] = 1.10; 95% confidence interval [CI] = 1.003-1.20) and increased odds of development of systemic sclerosis, vasculitis, or inflammatory myositis (OR = 1.23; 95% CI = 1.14-1.34). Interestingly military dust exposure appeared to be protective against development of systemic lupus erythematosus (OR = 0.81; 95% CI = 0.76-0.88) [38].

Recent studies suggest people in military service appear to be at increased risk of developing ReA, potentially for the reasons already discussed earlier in this paper [39,40].

Whilst rheumatic disease remained a common reason for disqualification from service in wars of the past, a recent study on Singaporean Military personnel with inflammatory arthritis concluded individuals with a good functional status could still potentially be deployed to perform active duty and this has significant implications for areas with an aging workforce [41].

However another large study of 657417 US army personnel noted a significantly increased risk of disqualification in individuals who held a diagnosis of Ankylosing Spondylitis, Psoriatic Arthritis, Systemic Lupus Erythematosus, or Rheumatoid Arthritis [42], however the authors noted a significant percentage of patients with these conditions were able to continue active service. More research to establish what factors differ between groups who are able to continue duties, compared to those who are disqualified is required.

In the past rheumatology's central role in military medicine lead one source to recommended: 'Provision should be made in all theatres that at least one officer, trained in the care of rheumatic diseases, on the medical staff of each hospital facility' [9]. Given the ongoing high prevalence of matters of rheumatological significance in military affairs, perhaps it is time to consider whether rheumatology should play a more central role, not just in combat and military medicine, but also in acute medicine generally.

Conclusion

This review demonstrates the importance military events have held in shaping the discipline of rheumatology. The close historical and ongoing association of rheumatology with war and military activity raises the question: should rheumatology be reintroduced into acute medicine practice and play a more central role in combat and military medical practice Globally?

Our current understandings of rheumatic disease entities and commonly used treatments have their origins in conflicts particularly those of the last 150 years.

The relationship of rheumatic diseases particularly to warfare that has led to modern rheumatologic practice can be summarised as follows:

- Large-scale warfare results in displacement of high numbers of people and movement of populations that frequently led in infectious disease outbreaks. Some of these events result in the development of post-infective arthritis, or even septic arthritis such as the arthritides of trench fever, gonococcal arthritis, syphilitic arthritis, tuberculosis-related joint disease, and many others.
- Military activities cause physical injuries that affect joints directly, or alternatively cause hastening of degenerative joint diseases in the form of post-traumatic arthritis, or early onset osteoarthritis.
- Physicians working closely with military personnel in armed conflict lead to the recognition of several disease entities such as:
 - o Complex regional pain syndrome which was first reported in soldiers of WWII.
 - o Psychological injury contributing to the development of rheumatic diseases including fibromyalgia in certain individuals was reported for the first time in soldiers of WWII.
- PTSD appears to be an independent risk factor for the development of inflammatory arthritis.
- Wartime chemical and biomedical research, directly and indirectly, resulted in the development of DMARDs that are commonly used in rheumatic clinical practice.

Clinical discoveries resulting from wars of the last 150 years have significantly contributed to the practice of rheumatology in civilian medical contexts ranging from an improved understanding of rheumatic disease presentations, the pathophysiology of disease processes, to a wide variety of treatments still commonly used today in rheumatology practice.

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