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Narrative Review

Defining the Osteoarthritis Patient: Back to the Future

by

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Abstract:

The history of osteoarthritis (OA) is important because it can help broaden our perspective on past and present controversies. The naming of OA, beginning with Heberden's nodes, is itself a fascinating story. According to Albert Hoffa, R. Llewellyn Jones and Archibald Edward Garrod, the name OA was introduced in the mid-19th century by surgeon Richard von Volkmann who distinguished it from rheumatoid arthritis and gout. Others preferred the terms 'chronical rheumatism', 'senile arthritis', 'hypertrophic arthritis' or 'arthritis deformans'. A similar narrative applies to the concept of OA affecting the whole joint vs. the 'wear-and-tear' hypothesis, inflammation and the role of the central nervous system (CNS). In the late 19th and early 20th centuries, the Garrods (father and son) and Hermann Senator argued that OA was a whole joint disease, and that inflammation played a major role in its progression. Garrod Jnr and John Spender also linked OA to a neurogenic lesion 'outside the joint'. The remaining 20th century was no less dynamic, with major advances in basic science, diagnostics, treatments, surgical interventions and technologies. Today, OA is characterized as a multi-disease with inflammation, immune and CNS dysfunction playing central roles in whole joint damage, injury progression, pain and disability. In the current 'omics' era (genomics, proteomics and metabolomics), we owe a great debt to past physicians and surgeons who dared to think 'outside-the-box' to explain and treat OA. Over 130 years later, despite these developments, we still don't fully understand the unravelling complexities of OA, and we still don't have a cure.

Key words:

osteoarthritis, history, inflammation, central nervous system, post-traumatic, pathophysiology

The disease called chronical rheumatism, which often passes under the general name of rheumatism and is sometimes supposed to be the gout, is in reality a very different distemper from the genuine gout and from the acute rheumatism, and ought to be carefully distinguished from both.

William Heberden (1816) [Heberden, 1816 #5001], Appendix, p 414

Osteoarthritis: Prevalence and Major Gaps

Osteoarthritis (OA) is one of the most prevalent and disabling chronic degenerative diseases and some predict a 7-fold increase by 2030 [Martel-Pelletier, 2016 #4984]. It affects over 250 million people worldwide, and impacts more than half of the over 65 population, with higher rates of disability in woman than men [Loeser, 2012 #4983;Martel-Pelletier, 2016 #4984]. Like many chronic diseases, the incidence of OA continues to rise from an ageing population, rapid rise in obesity, unhealthy dietary patterns, physical inactivity and chronic stress. [Pelletier, 2001 #4987;Loeser, 2012 #4983;Malemud, 2015 #4986;Kalaitzoglou, 2017 #4976;Warner, 2017 #5053]. There are many gaps in our understanding of OA, including the underlying drivers of its evolving pathophysiology, inflammation and the role of the central nervous system (CNS) [Loeser, 2012 #4983;Martel-Pelletier, 2016 #4984]. The aim of this narrative is to focus on some key characteristics that define the OA patient from a historical perspective to the present, and examine how many of the ongoing controversies were raised over 130 years ago. We also discuss the historical importance of a whole body systems-based approach to OA, which we believe is a key consideration for potential targets for future therapies.

What's in a name? The fight for OA's clinical and pathological independence

It is not to be expected that there should be agreement about the definition of anything until there is agreement about the thing itself.

John Stuart Mill (1806-1873)

In 1816, Heberden clearly understood that a distinction was necessary to describe his

“digitorum nodi” from gout and rheumatoid arthritis (RA) (Fig 1, see first quote above), however, he left it to others to formulate a name. It is often reported that the designation OA was introduced in 1890 by Sir Archibald Edward Garrod in his famous *A Treatise of Rheumatism and Rheumatoid Arthritis* [Dequeker, 2008 #4998]. However, Garrod placed the name 'osteo-arthritis' seventh on a list of eleven, and stated a preference for 'arthritis deformans' [Garrod, 1890 #5013] p234-5. The term OA appears to have originated earlier, in the mid-1850s, by one of the fathers of orthopedic surgery, Richard von Volkmann (1830-89) [Willy, 2008 #5099]. This new information was not recognized until the turn of the 20th century when von Volkmann's pioneering studies were revisited independently by Albert Hoffa (1859 –1907), R. Llewellyn Jones and Garrod himself [Jones, 1909 #5098; Jones, 1910 #5002; Garrod, 1910 #5000]. All three maintained that von Volkmann clearly differentiated OA lesions anatomically and pathologically from rheumatoid arthritis (RA) [Jones, 1909 #5098; Jones, 1910 #5002], *and showed that the initial changes in RA began in the synovial membrane, with cartilage deterioration being affected secondarily* [Jones, 1910 #5002]. According to Jones, von Volkmann's work underwent "an almost total eclipse" as the field was largely dominated by Charcot and Trastour's monograph (1853), which maintained that OA and RA were different 'grades' of the same entity, 'arthritis deformans' [Jones, 1910 #5002; Parish, 1963 #5003]. Charcot and Trastour's interpretation was endorsed and widely publicised by the authority Rudolph Virchow in his *Cellular Pathology* (1858) (Fig. 1). In the fullness of time, however, von Volkmann's sharp anatomic and pathologic distinctions were validated by other physicians and surgeons around the world including Hoffa, Hueter, Samaran, Waldmann, and Wollenberg [Jones, 1909 #5098].

On the question of designation, Benedek also points out that the term OA may have been proposed in 1863 by the Nomenclature Committee established by the Royal College of

Physicians of London [Benedek, 1999 #5095], which Garrod apparently referred to in his 1890 treatise. As a consequence of time to reach consensus for differentiating OA's primary bony/cartilagenous (osteo-) defect with secondary synovium complications from RA (infective and other variants), OA was not widely recognised as a distinct entity until the mid 20th century [Garrod, 1910 #5000;Parish, 1963 #5003] (Fig 1). Up until that time, 'arthritis deformans' remained the preferred term, with a number of less common names including *hypertrophic arthritis*, *chronic articular rheumatism*, *nodular rheumatism* and *senile arthritis* [Parish, 1963 #5003].

The changing faces of OA: from 'wear-and-tear' to inflammatory remodelling

Osteo-arthritis deformans is a chronic, proliferative, noninfectious inflammation, which gradually leads to progressive mutilation of the joint. The inflammation is due chiefly to altered and impaired function of the joint ... There may be mechanical trauma involving the joint directly or indirectly.

William H. Baur (1941) [Bauer, 1941 #4991] p129

In the modern literature, it is common to read that OA was traditionally viewed as a “wear-and-tear” disease, and that the concept of a whole joint disease was a recent concept [Pelletier, 2001 #4987;Robinson, 2016 #4979] (Fig 1). There is some support for this view, which at the turn of the 20th century was endorsed and widely circulated by eminent British surgeon Sir William Arbuthnot (1846-1943). Arbuthnot argued that OA progression was simply an age-dependent breakdown of articular cartilage, and should not be classified as a disease at all [Forsbrook, 1893 #5004;Burt, 1914 #5096]. However, the majority of physicians of the 20th century appear to have favored Garrod's 1924 account: "The lesions to which we apply the epithet osteo-arthritic, namely, *erosion of cartilages*, *the formation of osteophytes around the articular surfaces*, *eburnation of the bony surfaces and the like*, may result from any form of articular disease, provided that it be of sufficiently long standing." [Garrod, 1924 #5005]. Garrod's

emphasis on the whole joint, including adding a time dimension involving any form of articular disease, appears to argue against a simple 'wear-and-tear' erosion [Garrod, 1910 #5000; Bauer, 1941 #4991] (also see Bauer's quote above). More recently the 'wear-and-tear' scenario was raised again to serve as a backdrop for emphasising OA as a failure of the entire joint, which was analogous to heart, lung or kidney failure [Brandt, 2009 #4992; Loeser, 2012 #4983]. This analogy was pivotal as it shifted OA from being a whole joint phenomenon to a whole body systems defect.

The modern literature also abounds with claims that inflammation was a late concept in OA progression [Berenbaum, 2013 #4977]. This is only partly true. In the late 19th century, there were two schools of thought. Henry W. Fuller, Abraham Colles and Robert B. Todd believed OA was due to a "perversion of nutrition to tissues of the joints" with little or no active 'ordinary' inflammation [Forsbrook, 1893 #5004], whereas the Garrods, Hermann Senator and others, argued that inflammation was a key player with different temporal contributions [Forsbrook, 1893 #5004]. Within the second group, Garrod Jnr (AE) believed that the degenerative joint changes *preceded* the inflammatory contribution, whereas Hermann Senator argued it was partly degenerative and partly inflammatory [Forsbrook, 1893 #5004]. On reflection, one cannot help to be amazed by how insightful these past discussions were given their state of knowledge and paucity of quantitative methods.

Beyond the joint: OA as a neurogenic-immune homeostatic disorder.

Amongst those whose attention has been directed to diseases of the joints there is an impression, which is steadily gaining ground, that the disease which we know as rheumatoid arthritis, osteo-arthritis or arthritis deformans, is in an especial manner associated with some lesion of the central nervous system.

Archibald E. Garrod (1888) [Garrod, 1888 #5006]p89

From history, it is equally remarkable that a lesion of the CNS was proposed in OA and RA patients in the late 1880s. This linkage was inferred from the patient's higher resting heart rate, which implicated vagal nerve dysfunction [Garrod, 1888 #5006]. In a review of John Spender's book (1889) *The Early Symptoms And Early Treatment Of Osteoarthritis*, the following passage is revealing:

"The early symptoms are scientifically classed (by Spender) under four heads: 1) Increased velocity and tension of the heart's action; and here Spender suggests that the inhibitory action of the vagus was at fault. 2) The disturbance in the chromatogenous function of the skin. The patches of bronzing and discoloration are, Spender thinks, peculiar, and have been generally overlooked. 3) Vasomotor disturbances, as indicated by the clamminess of the skin and trophic changes, and 4) Specific neural symptoms." [Spender, 1889 #5018].

Along with joint space reduction, malalignment, subchondral bone thickening, ligament damage, pain, stiffness and disability, the clinical symptoms described by Spender continue to help define the OA patient today.

During the last century, the role of the CNS in OA progression has waxed and waned, which is most likely due to: 1) the complex evolving etiology of OA (and RA), and 2) lack of understanding of how the CNS communicates with the knee joint and different regions of the body. Progress was accelerated in the early 1950s when advances in electrophysiology, pharmacology and neural tracing techniques helped to track intricate neurohormonal feedback networks, including discovery of the hypothalamic-pituitary-adrenal axis, and the Nucleus Tractus Solitarius (NTS) located in the medulla [Ulrich-Lai, #5059;Heidt, 2014 #5043;Dobson, 2015 #4239] (Fig 2). The NTS continually receives signals from baroreceptors in the aortic arch and carotid sinus, and other inputs, and fine-tunes sympathetic-parasympathetic outflows to the body [Grill, 2009 #5063; Bonaz, 2016 #5010]. The outflow 'balance' helps to regulate heart-rate variability, ventricular-arterial coupling, tissue blood flow, venous capacitance, food intake, metabolism, and more recently, inflammation and immune status [Thayer, 2009 #3267;Tracey,

2009 #3245;Pawelec, 2014 #5057;Dobson, 2015 #4239;Straub, 2017 #5056].

More recently, it has been proposed that a slight imbalance to one or more of these CNS circuits may be associated with exacerbating the progression of many chronic diseases, like OA and RA, and distinct from the normal aging changes [Pawelec, 2014 #5057;Koopman, 2017 #5016;Galvez, 2017 #4937;Straub, 2017 #5056]. For example, subtle changes could occur to the CNS 'set-point' that controls whole body inflammatory 'tone' which may exacerbate OA progression and/or there could be subtle alterations to synaptic 'tuning' (inhibitory and excitatory) that may occur to a damaged joint, with their own injury and pain microcircuits feeding back into the central system [Kim, 2010 #5044;Turrigiano, 2012 #5046]. To illustrate the potential of bioelectronics therapeutics, Koopman and colleagues have recently showed that autonomic dysfunction (as measured by resting heart rate) *preceded and predicted* arthritis development in RA patients at risk of developing the seropositive disease [Koopman, 2017 #5016]. They further showed that vagus nerve stimulation, or pharmacological activation of the alpha7 subunit of nicotinic acetylcholine receptors, improved clinical signs and symptoms of RA, reduced cytokine production and protected against progressive joint destruction [Koopman, 2017 #5016]. Trials have not yet been carried out in OA patients, however, given that Driban and colleagues for the OA Initiative Investigators Group recently found that alpha-adrenergic blockers and beta-adrenergic blockers appeared to reduce structural changes and pain in the knee compared to non-users over a 24 month period, indicating less disease progression [Driban, 2016 #5076], the possibility exists by combining bioelectronic technologies with neuropharmacological agents, such as antiadrenergic drugs, may help to reduce OA progression.

Directions for Future Research: Towards a more systems-based approach

The measure of greatness in a scientific idea is the extent to which it stimulates thought and opens up new lines of research.

Despite more than 130 years of research, our understanding of the etiology and pathogenesis of OA remains incomplete and treatments have been largely unsuccessful. This is likely a consequence of the deep complexity and multi-faceted nature of OA, and too much reliance on a reductionist-type thinking. From history, it appears that as we invent new technologies, such as integrative genomics, proteomics, metabolomics and bioelectronics, there has been a tendency to drill down into the cell and seek single-nodal solutions, which may partly explain the failure of so many clinical trials [Dobson, 2014 #3702;Dobson, 2015 #4239]. Reductionism is important in breaking a system into its constituent parts; however, it does not do away with the system. A more whole body systems-based approach to OA research may help to develop new disease-modifying drugs and bioelectronic therapies [Mueller, 2017 #5097]. Moving from a 'whole joint-centric' view to a "whole body-centric" view involving the CNS, may redefine the OA patient but only time will tell.

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Ethics Approval and Consent to Participate

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Author contributions:

All authors contributed to the conception, design, implementation, data acquisition and analysis, writing and final approval of the manuscript.

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