Arthropy in art and the history of pain management—through the centuries to cyclooxygenase-2 inhibitors

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Abstract

Preserved human remains, artefacts and works of art contain records of the existence and prevalence of arthropathies, even in the absence of medical texts or formal written accounts, although these also exist for some epochs and cultures. Example objects from the Museum of Medical History in Brussels have been used to illustrate the magnitude of the burden of pain throughout the ages and how rheumatic diseases have indiscriminately afflicted people regardless of their positions in life or occupations. These include both osteoarthritis (OA) and rheumatoid arthritis (RA), as well as the seemingly ubiquitous gout and various skeletal deformities. Adequate pain management has been severely hampered, historically, by obstacles to a comprehensive and systematic classification of diseases posed by the social, religious and philosophical mores of the time, which made differential diagnosis almost impossible to achieve. However, despite this shortcoming, serendipitous events meant that precursors of modern medicines, such as willow bark extracts, were in routine use from the earliest recorded times. It has taken several millennia, however, before empirical treatment has given way to pharmacological rationale. The first clinically acceptable synthetic derivative of the active principle in willow, aspirin, became available only at the turn of the nineteenth century, while non-steroidal anti-inflammatory drugs (NSAIDs) did not arrive on the market until some 60 yr later. At the cusp of the twentieth and twenty-first centuries, physicians have a wider choice of analgesics available than ever before, including the cyclooxygenase-2 inhibitors, which represent the first major advance in NSAID development since the synthesis of the latter compounds themselves.

KEY WORDS: History of medicine, NSAIDs, Cyclooxygenase-2 inhibitors, Osteoarthritis, Rheumatoid, Arthritis, Art, Pain.

Introduction

Art and archaeology can be used to obtain new data, from which scientific, historical and epidemiological information can be extracted. This approach can be used to trace the occurrence of certain diseases in the past. For example, the earliest recorded case of ankylosing spondylitis was found in the 3000-yr-old Egyptian mummy of Ramses II [1]. The word 'arthritis' was used in both classic Greek and Roman literature, and evidence from historical medical texts has led to speculation that rheumatoid arthritis (RA) may have been a common disease as far back as the seventeenth century [2]. RA as a recognizable entity appeared in the Old World after the numerous exploratory travels of the sixteenth century [3], notably after the discovery of the New World by the seamen of Christopher Columbus. It could be speculated that these men brought back the triggering agent which then found a favourable biotope and susceptible hosts in Europe, who subsequently developed an aberrant immune reaction. However, there is evidence of the European antiquity of RA from osteo-archeological finds dating back to the Stone Age [4]. It could be that the absence of specific references to RA in texts and artefacts predating the voyage of Columbus is due to difficulties of interpretation and to a lack of systematic disease classification harking back to authors from classic antiquity, and that it is this non-Linnaean thinking that accounts for the apparent lack of RA, rather than a true epidemiological phenomenon.

RA was first adopted as a definitive term by Sir Alfred Baring Garrod in 1859 [5]. The term is derived from the Greek words ‘arthron’, meaning ‘joint’, and ‘rheuma’, meaning ‘flux’, the latter probably a reflection of the ‘equilibrium of humours’ hypothesis originally promul-
gated by Hippocrates and his contemporaries around 460 BC. Despite this nominal allusion to ancient theories, Garrod’s work shows that he had a sound understanding of the distinct associations and potential aetiologies of RA and gout. For his predecessors—and even among his contemporaries—classification of rheumatisms was based on a conceptual causative factor, with an explanation of pathogenesis that remained within the bounds of the Hippocratic tenets of Galen [6]. Thus the distinction between chronic gout and rheumatoid polyarthritis has not always been evident and at least some of the numerous references to gout in historical literature may, in fact, have reflected instances of RA.

A series of rheumatic conditions has struck the imagination of artists who not only reproduced what they saw, but also their creativity to express pain and changes in the quality of life (QOL). Paintings, sculptures, ceramics, sketches and writings depicting or describing medical deformities can be analysed not only through the lorgnette of the art historian, but also from the point of view of the rheumatologist.

Such historical epidemiological evidence can be found as far back as the pre-Columbian era (3000 BC–AD 1492) in ceramics showing injuries, hunchback and pain rictus, and in mummies that have been analysed using computer tomography (CT) scans and retrospectively diagnosed with osteoarthritis (OA) [7]. Evidence of arthropathological disease has been identified in Egyptian mummy heads [8] and also strongly suggested in Egyptian tomb art dating back to 1350 BC [9]. RA was frequently depicted in seventeenth century paintings by Rubens [3], who probably himself had chronic polyarthritis and may have found some cathartic relief through representation of the visible symptoms in his subjects. Many of his works clearly portray the ravages of RA, particularly those involving the hands and wrists. Renoir [10, 11] and Dufy [12] both had RA, and many other prominent figures from the spheres of the creative arts, politics and even sovereignty were afflicted by a variety of rheumatic diseases, of which gout appears most often [13–16]. This heritage opens up new avenues for research and discussion. When considered in parallel with the history of pain relief, notably the relatively recent development of non-steroidal anti-inflammatory drugs (NSAIDs) and, latterly, the arrival to market of their more specific successors, cyclooxygenase-2 inhibitors (coxibs), it is clear that throughout history many people with painful arthropathies would have benefited greatly had these compounds been available.

Rationale and methodology

From the permanent exhibition in the Museum of Medical History, Erasmus University Hospital, University of Brussels, relevant items were selected to show how the QOL of people living a few centuries ago, in a discrete geographical region and belonging to a specific culture, may have been affected by painful arthropathies and also, in some examples, by acute pain of a different origin. It is posited that their QOL would have been dramatically improved if NSAIDs, and especially the new coxibs, had been available.

Results of evaluation

The pre-Columbian era (3000 BC–AD 1492)

Tumaco expression of pain. Artists from the Tumaco region, situated along the coast and on the border between Columbia and Ecuador, paid much attention to depicting diseases, which were not considered a social handicap. Indeed, such imagery often adorned the attributes of power, such as jewellery, hats and breastplates (Fig. 1A). In these pieces (500 BC–AD 500), some subjects have one hand on the temporal region of the face, which is sometimes deformed by a rictus of pain and by wrinkles, signifying old age. For art historians, these details are consistent merely with signs of general ailment. For physicians, especially rheumatologists, this posture is reminiscent of the symptomatology associated with temporal arteritis, an inflammatory disorder frequently associated with polymyalgia rheumatica.

In terms of treatment, ancient pre-Columbian civilizations believed strongly in supernatural forces, both as a factor in disease aetiology and as a key tool in its management. Depicting deformity as art on everyday objects was designed to ‘transfer’ the disease from the affected individual to the item in question, thus effecting a cure. Many such artefacts have been discovered in ancient tombs and are thought to have had a shamanic purpose. There are no records regarding the efficacy of this therapeutic approach, although if successful, it might represent one of the earliest examples of the placebo effect.

The hunchback. The vase from Colima (300 BC–AD 200) shown in Fig. 1B depicts a human figure with a hump, being also small in stature and with short legs. From a medical perspective, a diagnosis of achondroplasia cannot be excluded. People with deformities were well accepted in ancient pre-Columbian society and often had a superior status in the group. With ageing, spinal deformities and achondroplasia can be associated with spinal stenosis, accompanied by low back pain radiating to the lower limbs. Pre-Columbians derived their remedies from medicinal plants and their health depended on the local flora. In Peru, for example, willow tree decoctions were used for the treatment of fever and rheumatism, constituting an early example of ‘NSAID analgesia’, albeit one based on serendipity and not on any understanding either of the aetiology of the disease, or of the mechanism of action of the treatment.

‘Rascar Capac’. A pre-Columbian mummy from Arica in Peru dating from the thirteenth century and given the name ‘Rascar Capac’ by the Belgian writer Georges Remy (alias Hergé, author of the cartoon series Tintin), had previously been examined by CT scanning [7]. A three-dimensional reconstruction (Fig. 1C) reveals degenerative changes of the right sacroiliac joint with a transitional anomaly of the right lumbosacral junction, signs consistent with OA. There is no direct evidence that
the anomaly caused pain, but if that had been the case, pre-Columbian civilisations are known to have treated rheumatic pain with a variety of interventions including multipuncture, cauterization, scarification, blood letting, massage, the application of coca leaves and thermo-sudotherapy [17]. It is likely that some or all of these
treatments would have been intrinsically painful and/or uncomfortable, and may have constituted examples of ‘the cure being worse than the disease’.

The Egyptian period (c. 1500 BC)

The decayed and abscessed teeth in an Egyptian mummy. Examination of Egyptian mummies frequently reveals pyorrhoea, decayed teeth and alveolar abscesses (Fig. 1D). One reason for this phenomenon is provided by the Egyptians’ practice of mixing mineral extracts with their food, thus producing dental abrasion. Cardamom extract and the ingestion of cooked mice were recommended for these problems, although likely efficacy of these interventions is, at best, questionable. Gum lesions were cauterized and the abscesses perforated for draining, both quite sound approaches as far as they went, albeit undoubtedly painful ones.

The Renaissance (1400–1590)

Sir John Falstaff. Sir John Falstaff is one of the most famous comic characters in English literature at the turn of the sixteenth century, appearing in four of Shakespeare’s plays. In an unsigned sketch (Fig. 1E), his left foot is wrapped and resting on a footstool. This is the typical representation of gout in English caricature.

Gout has been a prominent rheumatic condition throughout history, especially during the time of the Roman Empire, and according to Nriagu [18], saturnine gout probably contributed to the fall of the British Empire. Colchicum autumnale, used by Greco-Roman physicians and which had been abandoned as a treatment for some time because of its excessive purgative side-effects, came back into use at the beginning of the eighteenth century as the major component of a drink, Eau d’Husson (named after Nicolas Husson, a French officer who in 1783 boasted the efficacy of a ‘new’ secret remedy against gout).

‘The Dentist at Work’ by Theodore Rombouts (1597–1637)—an eighteenth-century engraving of a seventeenth-century painting. During the seventeenth century, Scultetus (1595–1645) developed new forceps (the cagnolo) which derived from Celsius’ instrument. These new forceps were able to lift the gum before extracting the tooth (Fig. 1F). However, no anaesthesia was available; decoctions of gum guaiac, derived from the New World tree Guaiacum officinale and containing as the active principle a monoethylic esther, guaiacol, and tobacco from the New World were used both as antiseptic and analgesics, and medicinal plant extracts were introduced into the ear since it was believed that the veins of the teeth went through the ear; or the ear was cauterized to block the vein and the pain.

‘Drawing of a hand with rheumatoid arthritis’ by Garrod. The Frenchman Landre-Beauvais is accredited reporting the first case of RA in 1800, but, as described earlier, the most sophisticated differential diagnosis between RA and gout was made by Sir Alfred Baring Garrod in 1859. In his treatise, The Nature and Treatment of Gout and Rheumatic Gout, Garrod points out the characteristic features of arthritis and the extra-articular involvement of RA, supported by an illustration showing a symptomatic hand (Fig. 1G). Garrod’s treatment plan included, notably, quinine sulphate, opium tincture and the application of leeches.

A brief history of pain and its management

The burden of pain through the ages

The impact of pain on mankind can be traced over the millennia, through depictions of pain states on archaeological artefacts, representations in art and literature and, latterly, descriptions of symptoms in scholarly and medical texts. Management of painful diseases long remained largely a reflection of the beliefs and attitudes of the time, rather than having any basis in physiological or pharmacological understanding. Religious, philosophical and political considerations were deeply influential on scientific thinking and practice [19]. Indeed, such factors are considered to be responsible for the many delays and wrong deductions of past epochs [20]. These have effectively postponed a proper understanding of pain aetiology—and hence of effective medical management—until relatively modern times. Even the etymological derivation of the word ‘pain’, from the Latin ‘peono’, meaning ‘punishment’, contains echoes of the prevalent attitude of the early Christian Church to pain—that it was synonymous with ‘sin and deserved suffering’—a premise that still lingers in a modern guise of ‘underestimation’ of its devastating impact and a frequently ‘stoical’ forebearance by its sufferers. This is particularly so for chronic pain states, for which medicine is only just beginning to find effective and essentially safe solutions.

Inflammation as a symptomatic and painful disease manifestation has been recorded from earliest antiquity. The oldest medical text on record, the Edwin Smith papyrus dating from Egypt 17 centuries before the birth of Christ, describes the body’s reaction to injury as ‘shememet’, the word always suffixed by a hieroglyph denoting ‘fire’, to symbolize the intrinsic redness and heat [21]. One thousand years later, Hippocrates termed inflammation ‘phlegmone’, or ‘the burning thing’, but the first definitive description, still in use in medicine today, is derived from the Roman author Cornelius Celsius writing in the first century AD: Rubor et tumor cum calore et dolore, that is, ‘redness and swelling with heat and pain’ [21].

Nomenclature and disease classification notwithstanding, it is certain that arthropathies have been associated with varying degrees of pain and disability throughout the history of humankind. Recent studies have shown that the majority of the total societal burden of pain comes from arthritis [22] and that chronic pain is a major and often disabling problem that impacts on patients’ QOL [22–24]. Since these observations have been made in a milieu of modern pharmacopoeias and strategic drug development, it can be conjectured that the historical and ancient burden of arthropathy-related pain was even
greater than that experienced today. It is well recorded that Renoir, for example, was so severely disabled by RA that he required a specially adapted chair and easel [13].

From ancient anodynes to analgesia today
The oldest known medical prescription, a 4000-yr-old small Babylonian clay tablet, makes reference to a revolting-sounding concoction of animal and plant extracts, supposedly effective for the easing of pain [25]. Ancient Egyptian physicians were among the first to postulate theories and mechanisms to explain pain [26]. They also described the presentation, diagnosis, and treatment of some painful conditions. For example, they practised a relatively sophisticated form of dentistry, including fillings, abscess drainage and fixation as ways to relieve severe toothache (see above). They also regularly used mixtures of plant origin as topical analgesics for stiff and painful joints [27], including Salix alba, a member of the willow family and ancient precursor of NSAIDs.

Already by the 1970s, Martindale's Extra Pharmacopoeia had devoted 240 pages to medications for pain relief and listed >1000 such preparations [25]. The twentieth century saw the development of several non-opioid analgesics. Phenacetin, which preceded the widespread use of aspirin, was subsequently withdrawn due to severe and sometimes fatal nephrotoxicity. It was succeeded by its much less toxic derivative, paracetamol (Panadol, Bayer), an agent still in regular use today for the management of mild-to-moderate pain, including muscular rheumatism, despite continuing debate and caution with regard to its hepatotoxic potential, specifically in overdosage.

Now, at the beginning of the third millennium, >30 different categories of analgesics, including NSAIDs and coxibs, are available to control pain and inflammation.

NSAIDs—latecomers in history
The forerunners of NSAIDs, aspirin and related compounds, remain the cornerstone treatment for arthritic diseases. Aspirin, or acetylsalicylic acid, is one of a broad group of compounds termed ‘salicylates’, that have their origins in several plant species, including willow (Salix spp.). Ancient Egyptians and Assyrians are known to have used willow extract to reduce the erythema and pain of inflamed joints, while the Roman Pliny, in the first century AD, prescribed the bark of another member of the willow family, the poplar, for the relief of sciatica [28]. But it was not until much later in history that the first NSAIDs—latecomers in history—were introduced. The severe gastrotoxicity associated with early efforts was a driving force in the subsequent development, by a father-and-son team of chemists working for Bayer, of acetylsalicylic acid [21], or aspirin per se, an entirely synthetic compound containing no willow derivatives [28]. Bayer Aspirin, as it was originally called, first entered clinical medicine in 1899 [32]. During the past century, it is estimated that one trillion aspirin tablets have been have been taken for a variety of indications, including pain relief [33].

Aspirin belongs to a class of drugs known as ‘anti-inflammatories’, more specifically, ‘non-steroidal anti-inflammatory drugs’, or NSAIDs. Arguably the most familiar, and the earliest of these, is indomethacin, which unlike earlier empirically derived agents was the product of pharmaceutical drug development and testing in animal models of inflammation [34]. Many more compounds of this type have since been synthesized, but despite extensive clinical use, their mechanism of action was not understood until the early 1970s, when Vane et al. determined that aspirin blocked the synthesis of a key inflammatory cytokine called prostaglandin E [35]. This seminal research paved the way for the development of other compounds with better efficacy and safety profiles, culminating in the novel class of agents called ‘coxibs’.

After Vane's work had been published, further research showed that NSAIDs inhibit prostaglandin synthetase, the enzyme that transforms arachidonic acid to prostaglandins [36]. This assertion was supported by the phenomenon of NSAID-induced gastrointestinal (GI) side effects, arising from their interference with the biosynthesis of those prostaglandins responsible for regulating stomach acid levels and maintaining the integrity of the gastric mucosa. More recently, two isoenzymes of prostaglandin synthetase have been identified, referred to as ‘cyclooxygenase-1’ (COX-1) and ‘cyclooxygenase-2’ (COX-2). Inhibition of COX-2 has been more directly implicated in mediating an anti-inflammatory effect, while conversely, inhibition of COX-1 has been linked with GI adverse events. Whereas non-specific NSAIDs inhibit both forms of the enzyme, coxibs are selective inhibitors of COX-2 and as such, should display equivalent efficacy to NSAIDs, but be better tolerated [37]. Clinical trials have indeed demonstrated similar efficacy [38] and a lower incidence of serious GI adverse events [38, 39] with coxibs.

Conclusions
Medical, archaeological and cultural records clearly show that numerous rheumatic diseases have afflicted humans since ancient times. This assertion is exemplified by items from the Museum of Medical History in Brussels. Religious doctrines, ancient philosophies scripted by influential figures, and associated factors precluded differential diagnosis and meant that historically,
accurate disease definitions were either completely absent or, at best, a somewhat 'hit and miss' science. Nevertheless, rheumatic disease in general is synonymous with swelling, fever, disability and chronic pain, all of which cause damaging changes to the affected person's QOL.

Clearly, the burden of pain in general and in relation to arthropathy in particular, has been considerable throughout the history of humankind.

Treatments have come and gone in the past, often coming tantalizingly close to the borders of efficacy based on pharmacological principles. For example, decoction of willow tree leaves containing salicylic acid as a treatment for gout and related disorders, mentioned at the beginning of the first millennium in the book of the Greek physician Dioscorides, was forgotten until 1763 [40]. This also happened with Colchicum extract, which was reintroduced into the clinical armamentarium in 1783 [40]. Today, physicians and rheumatologists have at their disposal a wider choice of analgesic and anti-inflammatory medicines than their predecessors could ever have dreamed possible and the most recent discoveries are better tolerated and offer a 10 yr improvement in QOL (Merck & Co., Inc., data on file). It is a pity for Job, Falstaff and Rascar Capac that such drugs were not available for them. The new generation of pain relief represents significant progress in the management of rheumatic conditions and in previous epochs they might have changed the face of the world.

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