# Arthritis: inflammatory or non-inflammatory?

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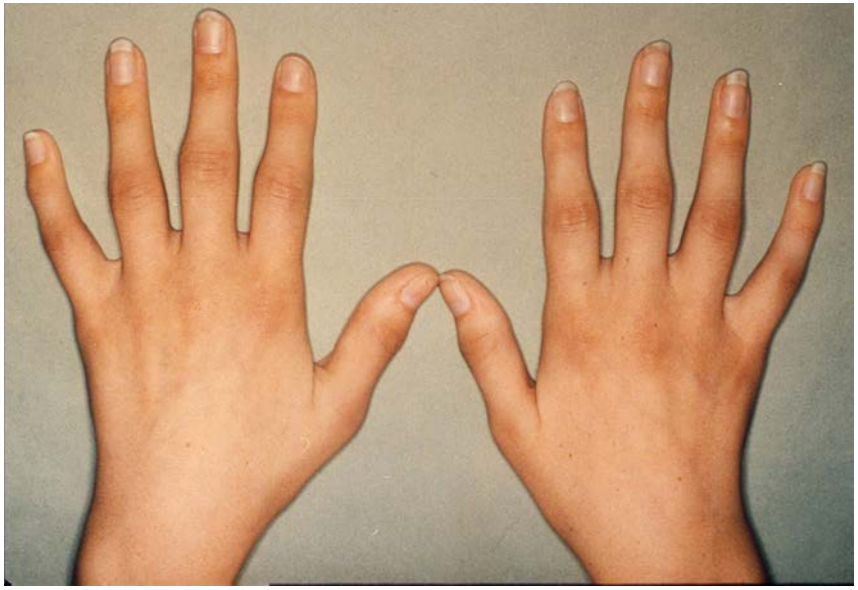
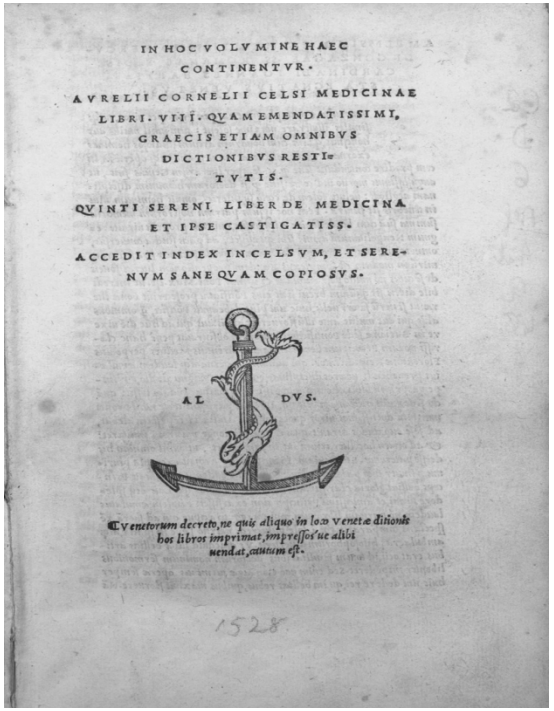
# What is arthritis?



# Aulus Cornelius Celsus, Roman Encyclopedist, 25 B.C. - 50 A.D. De Medicina



IN HOC VOLVMINE HAEC
CONTINENTVR.

AVRELII CORNELII CELSI MEDICINAE
LIBRI. VIII. QVAM EMENDATISSIMI,
GRAECIS ETIAM OMNIBVS
DICTIONIBVS RESTI-
TVTIS.

QVINTI SERENI LIBER DE MEDICINA
ET IPSE CASTIGATISS.

ACCEDIT INDEX IN CELSVM, ET SERE-
NVM SANE QVAM COPIOSVS.

AL DVS.

Venetorum decreto, ne quis aliquo in loco venetæ ditionis
hos libros imprimat, impressos ue alibi
uendat, cautum est.

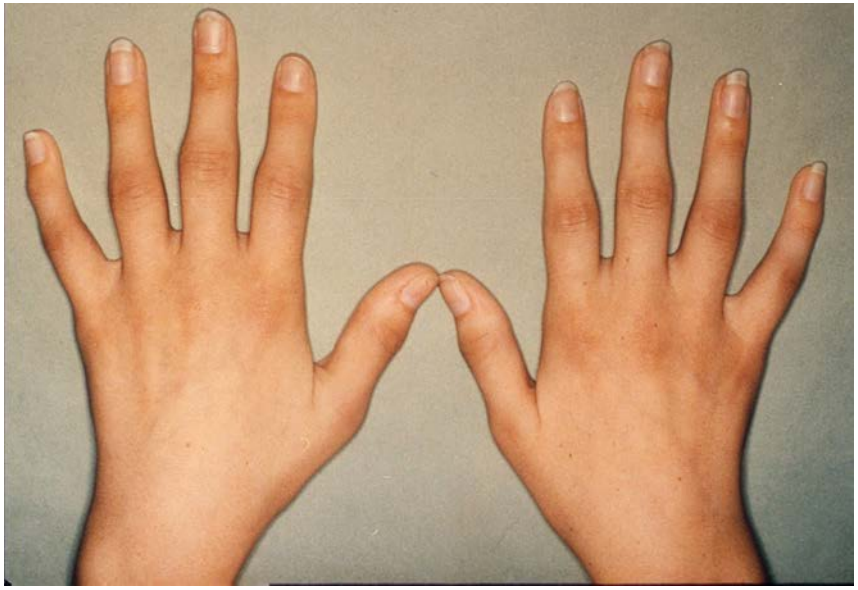
1528

- Calor – heat
- Rubor – redness
- Tumor – swelling
- Dolor – pain

- Functio laesa – loss of function

Rudolph Virchow
Father of Modern Pathology

# Inflammation of joint(s)



# Inflammation? True!

Mediators Inflamm. 2014;2014:561459. doi: 10.1155/2014/561459. Epub 2014 Apr 30.

**The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis**

Wojdasiewicz P[1], Poniatowski ŁA[1], Szukiewicz D[1]

## Abstract

Osteoarthritis (OA) is the most common chronic disease of human joints. The basis of pathologic changes involves all the tissues forming the joint; already, at an early stage, it has the nature of inflammation with varying degrees of severity. An analysis of the complex relationships indicates that the processes taking place inside the joint are not merely a set that (seemingly) only includes catabolic effects. Apart from them, anti-inflammatory anabolic processes also occur continually. These phenomena are driven by various mediators, of which the key role is attributed to the interactions within the cytokine network. The most important group controlling the disease seems to be inflammatory cytokines, including **IL-1 β , TNF α , IL-6, IL-15, IL-17, and IL-18**. The second group with antagonistic effect is formed by cytokines known as anti-inflammatory cytokines such as IL-4, IL-10, and IL-13. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of OA with respect to inter- and intracellular signaling pathways is still under investigation. This paper summarizes the current state of knowledge. The cytokine network in OA is put in the context of cells involved in this degenerative joint disease. The possibilities for further implementation of new therapeutic strategies in OA are also pointed.

Curr Pharm Des. 2015;21(17):2206-15.

**Biological therapies in osteoarthritis**

Wenham CY, McDermott M, Conaghan PG[1]

## Abstract

Given the paucity of effective therapies and the increasing prevalence of osteoarthritis (OA) with ageing and overweight populations, new therapies for this painful, life-impairing condition are desperately needed, for both symptom relief and structural modification. With a growing understanding that OA involves multiple tissue pathologies including inflammation, many more therapeutic targets have been identified. This review will provide a current overview on the role of biologics in OA, including anti-tumour necrosis factor agents, growth factors and interleukin-1 antagonists.

Yonsei Med J. 2015 Sep;56(5):1379-83. doi: 10.3349/ymj.2015.56.5.1379.

# Efficacy of Direct Injection of Etanercept into Knee Joints for Pain in Moderate and Severe Knee Osteoarthritis

Ohtori S[1], Orita S[2], Yamauchi K[2], Eguchi Y[2], Ochiai N[2], Kishida S[2], Kuniyoshi K[2], Aoki Y[2], Nakamura J[2], Ishikawa T[2], Miyagi M[2], Kamoda H[2], Suzuki M[2], Kubota G[2], Sakuma Y[2], Oikawa Y[2], Inage K[2], Sainoh T[2], Sato J[2], Shiga Y[2], Abe K[2], Fujimoto K[2], Kanamoto H[2], Toyone T[2], Inoue G[2], Takahashi K[2]

## Abstract

**PURPOSE:**

Osteoarthritic (OA) pain is largely considered to be inflammatory pain. However, during the last stage of knee OA, sensory nerve fibers in the knee are shown to be significantly damaged when the subchondral bone junction is destroyed, and this can induce neuropathic pain. Several authors have reported that tumor necrosis factor-α (TNFα) in a knee joint plays a crucial role in pain modulation. The purpose of the current study was to evaluate the efficacy of etanercept, a TNFα inhibitor, for pain in knee OA.

**MATERIALS AND METHODS:**

Thirty-nine patients with knee OA and a 2-4 Kellgren-Lawrence grading were evaluated in this prospective study. Patients were divided into two groups; hyaluronic acid (HA) and etanercept injection. All patients received a single injection into the knee. Pain scores were evaluated before and 4 weeks after injection using a visual analogue scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and they were compared between the groups.

**RESULTS:**

Before injection, VAS and WOMAC scores were not significantly different between the groups ($p>0.05$). Significant pain relief was found in the etanercept group at 1 and 2 weeks by VAS, and at 4 weeks by WOMAC score, compared with the HA group ($p<0.05$). No adverse events were observed in either group.

**CONCLUSION:**

Direct injection of etanercept into OA knee joints was an effective treatment for pain in moderate and severe OA patients. Furthermore, this finding suggests that TNFα is one factor that induces OA pain.

J Orthop Res. 2016 Apr;34(4):650-7. doi: 10.1002/jor.23069. Epub 2015 Oct 26.

# Sulfasalazine attenuates ACL transection and medial menisectomy-induced cartilage destruction by inhibition of cystine/glutamate antiporter

Tsai WY[1], Tsai RY[2], Liu CC[3,4], Wu JL[5,6], Wong CS[1,7,8,9]

## Abstract

We had previously demonstrated that excitatory amino acid glutamate plays a role in the progression and severity of knee osteoarthritis (OA), and early hyaluronic acid injection attenuates the OA progression by attenuation of knee joint glutamate level, which was also related to the cystine/glutamate antiporter system X (system XC-) expression. System XC- uptakes cystine into chondrocytes for glutathione (GSH) synthesis, but the role of system XC- in OA is rarely addressed. Sulfasalazine (SSZ) is a system XC- inhibitor; SSZ was applied intra-articularly to study the function of system XC- in the development of OA in rats subjected to anterior cruciate ligament transection and medial meniscectomy (ACLT + MMx). Moerover, the system XC- activator N-acetylcysteine (NAC) was also applied to verify the role of system XC-. The intra-articular injection of SSZ significantly attenuated knee swelling and cartilage destruction in the knees of ACLT + MMx rats and this effect was blocked by NAC. The results showed that inhibition of system XC- function can attenuate ACLT + MMx-induced cartilage destruction. In the present study, system XC- inhibitor SSZ was shown to reduce glutamate content in synovial fluid and GSH in chondrocytes. It was also showed SSZ could attenuate ACLT + MMx-induced cartilage destruction, and treatment of NAC reversed the protective effect of SSZ.

# Case history-1

- 32-year-old, banker
- Low back pain 2 months, more in evening
- Better on off days

- BMI 29.3 kg/$m^2$
- Mechanical back pain
- Avoid bad postures, breaks
- Weight reduction

- Better

# Case history-2

- 35- year-old, male
- Low back pain 3 months, more in morning
- More in off days
- No skin, mucosal or eye lesion
- Modified Schobar's test - positive

- ESR 72 mm/1$^{st}$ hr
- CRP 48 mg/L
- X-ray SI joints – sclerosis
- HLA B-27 +ve

- Naproxen
- Sulphasalazine

- Azoospermia

# Why this differentiation?

- Clinical reasoning/diagnosis
- Investigation plan
- Treatment
- Monitoring
- Outcome/prognosis

# At the onset

- Age
- Sex
- Occupation
- Joint(s)/area
- Family history
- Features of inflammation
- Extra-articular features
- Systemic features
- Examination
- Lab
- Imaging
- Rx/monitoring
- Pregnancy

# *Thank you all*