Causes and treatment of joint pain
Aims

• Major rheumatic conditions
  1. Autoimmune
  2. crystal-related
  3. ‘degenerative’

• Origins of joint pain - inflammatory or damage-related

• Therapeutic options
  1. Analgesia (simple, NSAIDs)
  2. Disease modifying (MTX, biologicals)
  3. Corticosteroids

• Industrial placement opportunity
Therapeutic aims

↓ Pain
↓ Stiffness
↓ progressive joint damage

? Repair joint damage

Maintain functional capacity and quality of life
Origin of joint pain; inflammatory or non-inflammatory?

**Inflammatory**: redness, heat, pain, swelling and loss of function

Symptoms worse in morning
Eased by exercise

**Non-inflammatory** joint pain

Worse in evening
Exacerbated by use
**Origin of pain: Inflammation and tissue damage coexist**

<table>
<thead>
<tr>
<th></th>
<th>Inflammation</th>
<th>Tissue damage</th>
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</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Polymyalgia</td>
<td>++++</td>
<td>-</td>
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<tr>
<td>Crystals (eg gout)</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Osteoarthritis</td>
<td>++</td>
<td>++++</td>
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</tbody>
</table>
Relationship between inflammation and tissue damage

- Cellular activation, migration, adhesion & protease expression
- Immune activation via DAMPs
Rheumatoid arthritis

- Autoimmune disease - 1% prevalence, M:F 2.5:1

- Multifactorial
  - Environmental - smoking↑, alcohol↓
  - Genetics - Heritability 60%,
    - >100 loci identified (p<0.5x10^{-8})
Disease progression in RA

Inflammation (CRP) x time = damage

Rheumatology 2008 47:392-398
Radiological damage in RA

- Modified Larsen score
- 32 joints of hands & feet
- Score 0-160

Radiological damage in RA

Genetic of Rheumatoid Arthritis (GoRA) study
1,007 patients attending Rheum OP (Sheffield)
Analgesia

Paracetamol 1gm qid (prn)

Paracetamol/codeine preparations

Non-steroidal anti-inflammatory drugs (NSAIDS)
  Cyclooxygenase inhibition

Opioid derivatives
## Classification of NSAIDs

<table>
<thead>
<tr>
<th>Groups</th>
<th>Acetysalicylic acid</th>
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<tbody>
<tr>
<td>Salicylic acids</td>
<td></td>
</tr>
<tr>
<td>Acetic acids</td>
<td>Diclofenac</td>
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<tr>
<td></td>
<td>Etodolac</td>
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<td></td>
<td>Indomethacin</td>
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<tr>
<td>Propionic acid</td>
<td>Ibuprofen</td>
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<tr>
<td></td>
<td>Naprosyn</td>
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<tr>
<td>Enolic acids</td>
<td>Phenylbutazone</td>
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<tr>
<td></td>
<td>Meloxicam</td>
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<tr>
<td></td>
<td>Piroxicam</td>
</tr>
<tr>
<td>COX-2 specific</td>
<td>Celecoxib</td>
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<td></td>
<td>Etoricoxib</td>
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</tbody>
</table>
## NSAIDs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>COX 1</th>
<th>COX 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Constitutive</td>
<td>Inflammation-induced</td>
</tr>
<tr>
<td>Function</td>
<td>Physiological prostaglandins: vascular tone, gastric protection, renal function</td>
<td>Proinflammatory prostagladins eg PGE(_2) and PGI(_2)</td>
</tr>
<tr>
<td>Inhibition by NSAIDs</td>
<td>COX 1</td>
<td>COX 2</td>
</tr>
<tr>
<td></td>
<td>Indomethacin, Aspirin, Ibuprofen, Diclofenac</td>
<td>Coxibs</td>
</tr>
</tbody>
</table>
All NSAIDs associated with increased cardiovascular risk
Naprosyn seems least harmful

BMJ 2011;342:c7086.
Anti-inflammatory treatments - corticosteroids

Potent anti-inflammatory agents

Down-regulate production of many inflammatory molecules

Hydrocortisone (produced by adrenal) is short acting

Act through specific cytoplasmic receptors

Disease modifying - reduce CRP and x-ray progression

Oral, intra-muscular or intra-articular
Anti-inflammatory treatment: Disease-modifying antirheumatic drugs (DMARDs)

• Slow onset (6 weeks +)

• Systemic inflammatory response (CRP)

• Improve functional status

• Slow radiological progression

• Monotherapy or combination

• Use at onset since early 1990s v after 2-3 yrs 1980s

• Hydroxychloroquine, sulphasalazine, methotrexate
Anti-inflammatory treatments: biological agents

Anti-TNF agents: infliximab, etanercept, adalimumab, golimumab, certulizumab

Anti-IL-6: tocilizumab

Anti-IL-17: secukinumab

Anti-IL12/23: ustekinumab

B cell depletion: rituximab

Immune cell cross-talk: abatacept
Treatment of early RA

**Initial**

Analgesia - paracetamol ± codeine
- NSAID

Anti-inflammatory - corticosteroids im
- methotrexate/suphasalazine

Treat to target - nurse led clinics

Add 2nd DMARD if poor response

Add biological agent
Osteoarthritis

Age-related ‘wear and tear’ arthritis

Hands, spine, hips, knees, 1st toes commonly

3 main components:  
   i. cartilage loss  
   ii. bone sclerosis and osteophytes  
   iii. inflammation (especially early)

No disease modifying treatment except weight loss

Treatments:  
   simple analgesia  
   NSAIDs  
   intra-articular steroids (if inflammed)  
   Joint replacement

Lancet 2005,365;965-73
Poor correlation between structural damage and joint pain in OA

Pain is primary clinical symptom in OA

Origin and mechanism of pain in OA poorly understood

Frequent discordance between OA tissue damage and joint pain

Variants in pain pathway genes associated with asymptomatic versus symptomatic OA

*COMT*, *SCN9A* and *TRPV1*
Gout

Acute episodes of arthritis

NLRP3 inflammasome activation by uric acid crystals

Extreme joint pain is the central feature

High serum uric acid and crystals in joint aspirate

Patient frequently reports:
1. Unable to weight bear
2. Cannot put bedclothes over foot
3. Pain exacerbated by movement of others in locality
Pain management in acute gout

NSAIDs

Corticosteroids orally or intra-articular

Colchicine - inhibits microtubule formation resulting in:

I. ↓ NLRP3 activation
II. ↓ NFκB activation
III. ↓ adhesion molecule expression on endothelium
IV. ↓ superoxide radicle production
Fibromyalgia

Chronic widespread pain

Prevalence of 2% to 8%

Accompanied by fatigue, memory problems, and sleep disturbances

Not related to inflammation or tissue damage
What is fibromyalgia?

Fibromyalgia is a condition that causes widespread pain. It’s not life-threatening or progressive but it can still have a major impact on your quality of life. In this booklet we’ll explain the symptoms and possible causes and look at how fibromyalgia can be treated. We’ll also suggest where you can find out more about living with fibromyalgia.

At the back of this booklet you'll find a brief glossary of medical terms — we've underlined these when they're first used.

www.arthritisresearchuk.org

localised muscular/joint pain

disease, illness

anxiety, life crisis

SLEEP DISTURBANCE

insufficient deep restorative sleep

difficulty with daily activities, fatigue, widespread muscular pain and tenderness
Living with Fibromyalgia

Fibromyalgia Tender Points

Front

Back
EULAR management recommendations of fibromyalgia

Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context.

Fibromyalgia should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features.

Optimal treatment requires a multidisciplinary approach including non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features, such as depression, fatigue and sleep disturbance in discussion with the patient.

Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia.

Corticosteroids and strong opioids are not recommended.

Antidepressants/pregabalin frequently used

Exercise, hydrotherapy, cognitive behavioural therapy

*Ann Rheum Dis* 2008;67:536-541
Summary

• Joint pain arises from inflammation and/or tissue damage

• Rapid resolution of inflammation reduces pain and prevents tissue damage

• Revolutionary therapeutic advances over past 20 years for inflammatory joint diseases

• Major area of unmet need in understanding causes of fibromyalgia

• Osteoarthritis increasing prevalence with no disease-modifying treatments
Industrial collaboration opportunity: pain research

Asahi Kasei Pharma - JAPAN

Starting from April 2017 we would like to send a Guest Researcher for 1 year to a facility that has a focus on running clinical trials and evaluating pain.

The general objectives for sending out a Guest Researcher to be hosted at a Pain Research Group are:

1. To understand how to run a clinical trial in a pain indication in a global context
2. To understand how to put a protocol together to run a successful pain study (and to understand the differences between a protocol being established in Japan vs a global setting)
3. To understand specific pain assessment tools and the advantages and disadvantages of each
4. To understand which pain assessment tools to implement in which type of protocol
5. To establish relationships with pain related research teams around the globe

The proposed candidate will hold a Master’s degree and will have worked in Asahi Kasei Pharma for no longer than 5 years since graduating university. As they are native Japanese, they will also be sent to intensive English school before joining the host research team.