Rheumatology – learning from the past. ‘science and serendipity’

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Science and serendipity

- History
- Rheumatology Department
- Disease understanding
- Drug development and science
Serendipity

a "fortunate happenstance" or "pleasant surprise". It was coined by Horace Walpole in 1754.

The notion of serendipity is a common occurrence throughout the history of scientific innovation.

Alexander Fleming's accidental discovery of penicillin in 1928.
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Rheumatology – from workhouse to 1969
Rheumatology Department

1949 Appointment of Dr LM Jennings
  ‘for the treatment of chronic rheumatism’
1985  Dr Anthony Bradlow
1992  Dr Joel David
2001  Dr Jeremy McNally
2009  Dr Antoni Chan
2012  Dr Gordon MacDonald
2014  Dr Jo Kitchen
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The Evolving management of RA

- **1591**: “Rheumatism” (Guillaume de Baillou)
- **1859a**: “Rheumatoid Arthritis” (Sir Alfred Garrod)
- **1860s**: Quinine
- **1890s**: Willow Bark
- **1920s**: Aspirin
- **1940s**: Gold Injections
- **1980s**: Steroids
- **1990s**: Methotrexate (MTX)
- **1990s**: Biologics

Drugs in Rheumatology

1949 – Philip Hench and Edward Kendall first used **cortisone** in autoimmune diseases
1935  Gold salts were used for RA (cryotherapy / aurotherapy)

1980  Methotrexate tried in 33 patients with RA  
(Approved for use in 1988)
History of Rheumatology

1959 – Charnley hip replacement
What causes arthritis?
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Higher-level immune regulation and immune senescence

GM-CSF
Anti-TNF
Anakinra
Tocilizumab

Synovial Inflammation

Extracellular matrix proteins

Destructive changes

Systemic inflammation

Temperature (°C)
Time

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Anti-TNF alpha treatment (biologic therapy)
Rheumatoid arthritis

- Chronic inflammatory arthritis
- Affects 0.8-1.0% of the population in the UK
- 3 times commoner in women
- Can affect any age - usually starts 40-60 years
- 1/3 stop work within 2 years of onset

- Total cost of RA in the UK is £3.8 to £4.75 billion per year
Rheumatoid Arthritis
Rheumatoid arthritis

- Pre-clinical Disease
  - Acute inflammation
    - Persists, spreads, damages
      - Chronic Disease – DAMAGE and DISABILITY

Early Treatment
What about smoking?’
Rheumatoid arthritis - smoking

- Primary and secondary prevention

- Smokers develop severe RA

- DMARDs work less well in smokers

- Biologics work less well in smokers
RF and Anti-CCP Production Precede the Onset in About 50% of Patients with RA

Cumulative frequency of patients with IgM-RF or anti-CCP before the onset of RA indicates early humoral activation.¹

Serologic Analysis of 98 Patients with RA and 232 Control Patients.²

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<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Anti-CCP</td>
<td>41%</td>
<td>97.8%</td>
</tr>
<tr>
<td>RF</td>
<td>62%</td>
<td>84%</td>
</tr>
<tr>
<td>Combination of anti-CCP and RF</td>
<td>99.6%</td>
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Rheumatoid arthritis

- Pre-clinical Disease
  - Acute inflammation
    - Persists, spreads, damages
    - Chronic Disease – DAMAGE and DISABILITY

Early Treatment
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The S factor

Have you got... The S factor?

Stiffness
- Early morning joint stiffness lasting over 30 minutes

Swelling
- Persistent swelling of one joint or more, especially hand joints

Squeezing
- Squeezing the joints is painful in inflammatory arthritis

This could be inflammatory arthritis
Rheumatoid arthritis

• Education – GP and patients

• Early Arthritis Clinics

• Treat to Target (T2T)

• Remission induction / maintenance therapy
Course of RA Over 30 Years: Schematic Representation

Severity (Arbitrary Units)

- Inflammation
- Disability
- Radiographs

Duration of Disease (Years)

Therapies for Active Rheumatoid Arthritis after Methotrexate Failure


CONCLUSIONS
With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxychloroquine added to methotrexate, was no inferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy. (Funded by the Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, and others; CSP 551 RACAT ClinicalTrials.gov number, NCT00405275.)
Summary

• Learn from the past.
• Innovate from bench to bedside
• Early detection / prevention - aggressive treatment
• Remission is the mission (DMARDs/Biologics/T2T)
• ‘Personalised’ medicine (targeted therapies)
Thank you.

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Rheumatology Update

Early Arthritis Clinic
Ultrasound Biologic Therapy

Dr Jo Kitchen, M.D., MRCP
Consultant Rheumatologist
Rheumatology

- Investigation, diagnosis and management of patients with arthritis and other musculoskeletal conditions.
- Rapidly evolving specialty
- Advancements owing largely to new scientific discoveries about the immunology of these disorders.
- “Autoimmune diseases”.
Osteoarthritis - Primary Care
Tailor treatment based on individual patient characteristics.
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Inflammatory Arthritis

Normal joint vs. Rheumatoid arthritis and Osteoarthritis
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Normal

Rheumatoid

Strand et al. Nature Reviews Drug Discovery 6, 75–92 (January 2007) | doi:10.1038/nrd2196
Psoriatic arthritis
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TOO LATE!
Even a Brief Delay in Starting DMARD Therapy Can Affect Radiographic Outcome

Treating 15 Days After First Visit Resulted in Better Radiographic Outcomes at 2 Years

Median Sharp Score

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Early Arthritis clinics
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Multidisciplinary Team

Specialist Nurse

Physiotherapist

Occupational Therapist

Arthritis Research UK
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Normal Finger joint on ultrasound

Tendon
Metacarpal bone
Proximal phalanx
JS
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**Normal Finger joint on ultrasound**

- Subcutaneous tissue
- Tendon
- Cartilage
- Metacarpal bone
- Proximal phalanx
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Musculoskeletal Ultrasound

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Inflammation in the wrist

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Greyscale

Doppler
Disease Modifying Anti-Rheumatic Drugs
Biologic therapies
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- Infliximab
- Adalimumab
- Golimumab
- Certolizumab
- Etanercept
- Abatacept
- Tocilizumab

TNF
- Antibody
- Chimera
- Human
- Human
- Humanized Pegylated
- Fusion protein
- Human protein
- Humanized

IL-6R
- Recombinant human Variable region
- Human constant region like protein
- Human fusion protein
- Human variable region
- Mouse variable region
- Polyethyleneglycol
- Human constant region
Anti-TNF Biologic Treatments

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Other Biologic Therapies
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MabThera®
B CELL THERAPY. LASTING SUCCESS.

Orencia®
(abatacept)

RoACTEMRA®
tocilizumab
Current Therapies
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Patient group

Drug toxic but beneficial

Same diagnosis, same prescription

Drug NOT toxic and NOT beneficial

Drug toxic but NOT beneficial

Drug NOT toxic and beneficial

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Benefits of Ultrasound

- Early (same day) diagnosis
- Monitoring response
- Assessing activity
- Guided injections