From wax to JAKs: Two decades of advances in rheumatology

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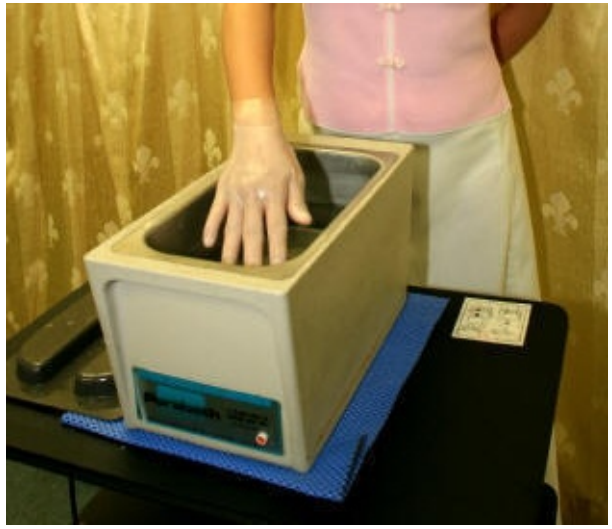
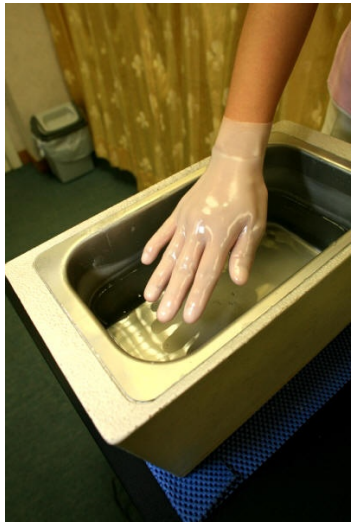
Wax therapy for arthritis





High dose aspirin as an NSAID

The Facts about Aspirin

The Bayer Cross—
Your Guarantee of Purity

BAYER

Bayer-Tablets and Capsules of Aspirin may be purchased and used with full confidence—

Because: Every officer and director of The Bayer Company, Inc., is an *American*.

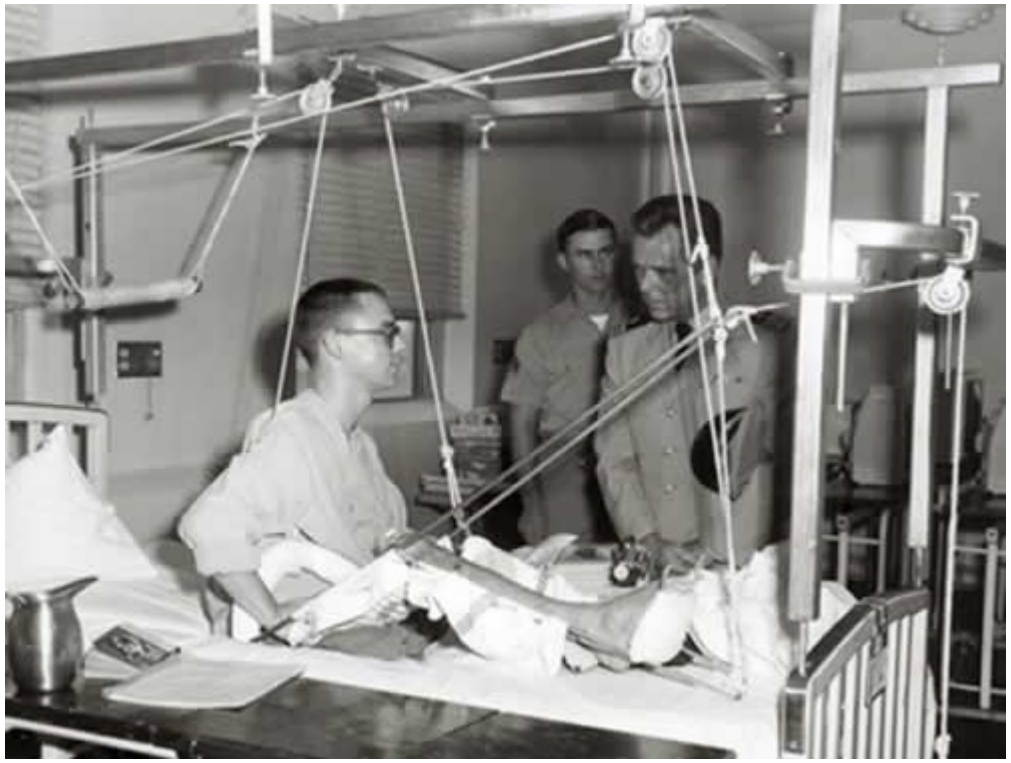
Because: Bayer-Tablets and Capsules of Aspirin contain *genuine* Aspirin, which has been made in America—on the banks of the Hudson—since 1904.

Because: Every package and *every tablet* of genuine Bayer-Tablets and Capsules of Aspirin is invariably marked for identification and also for your additional protection with The Bayer Cross.

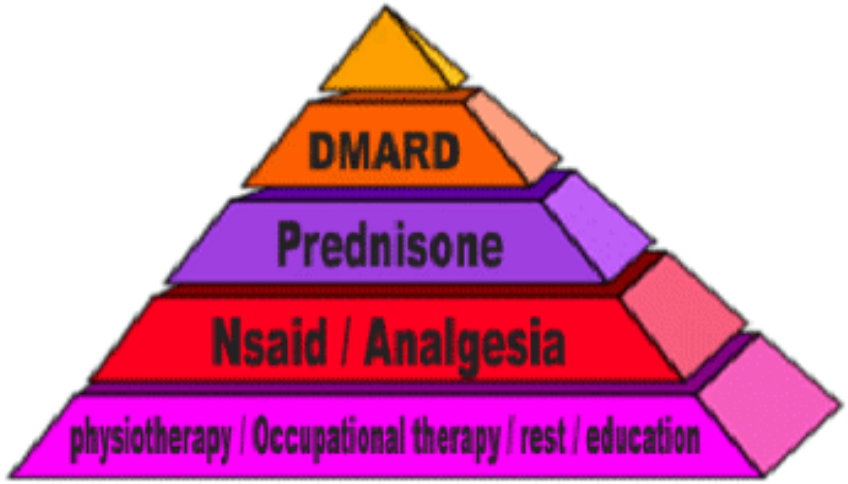
The trade-mark "Aspirin" (Reg. U. S. Pat. Office) is a guarantee that the monoaceticacidester of salicylicacid in these tablets and capsules is of the reliable Bayer manufacture.

Bayer-Tablets of Aspirin

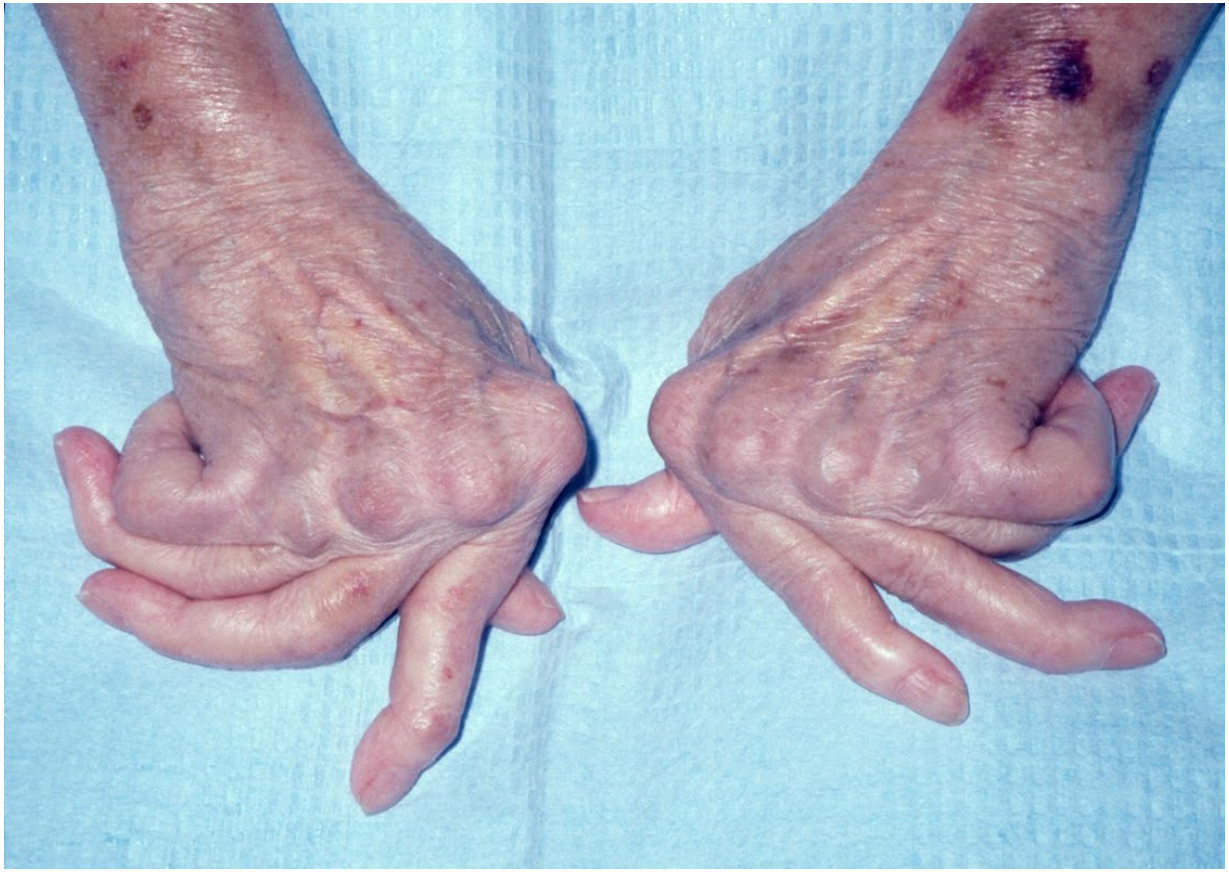
Traction for low back pain



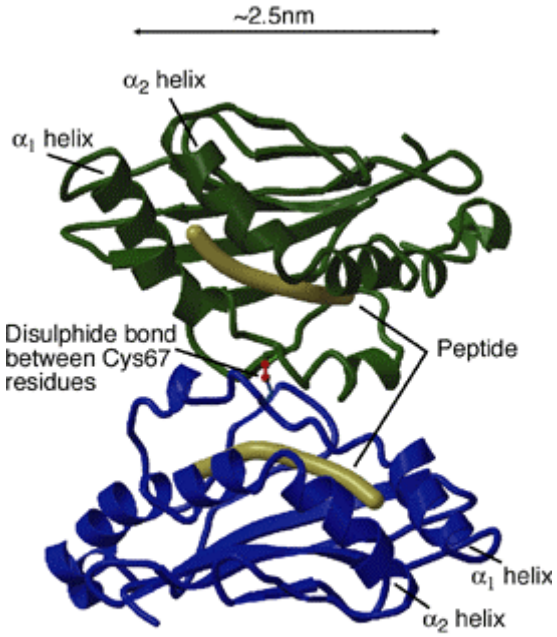
The treatment pyramid



The result of the treatment pyramid

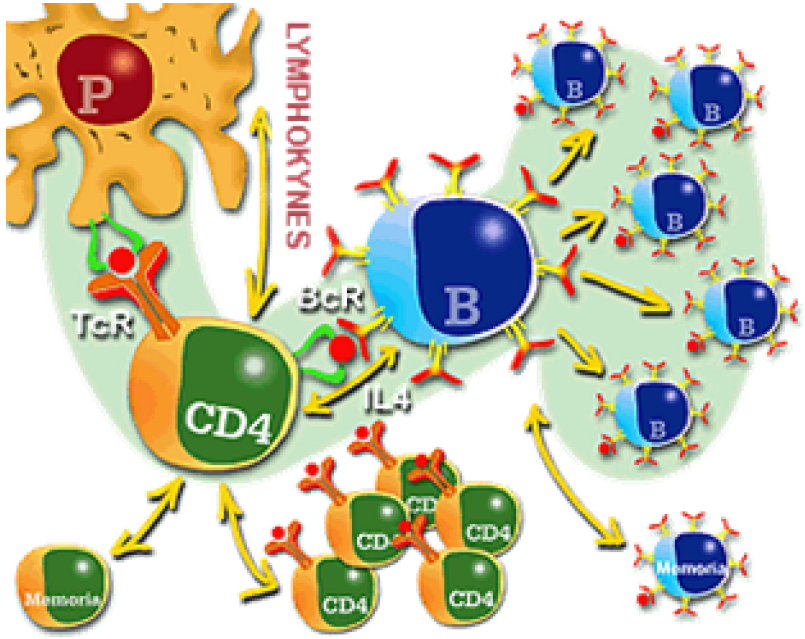


HLA-B27

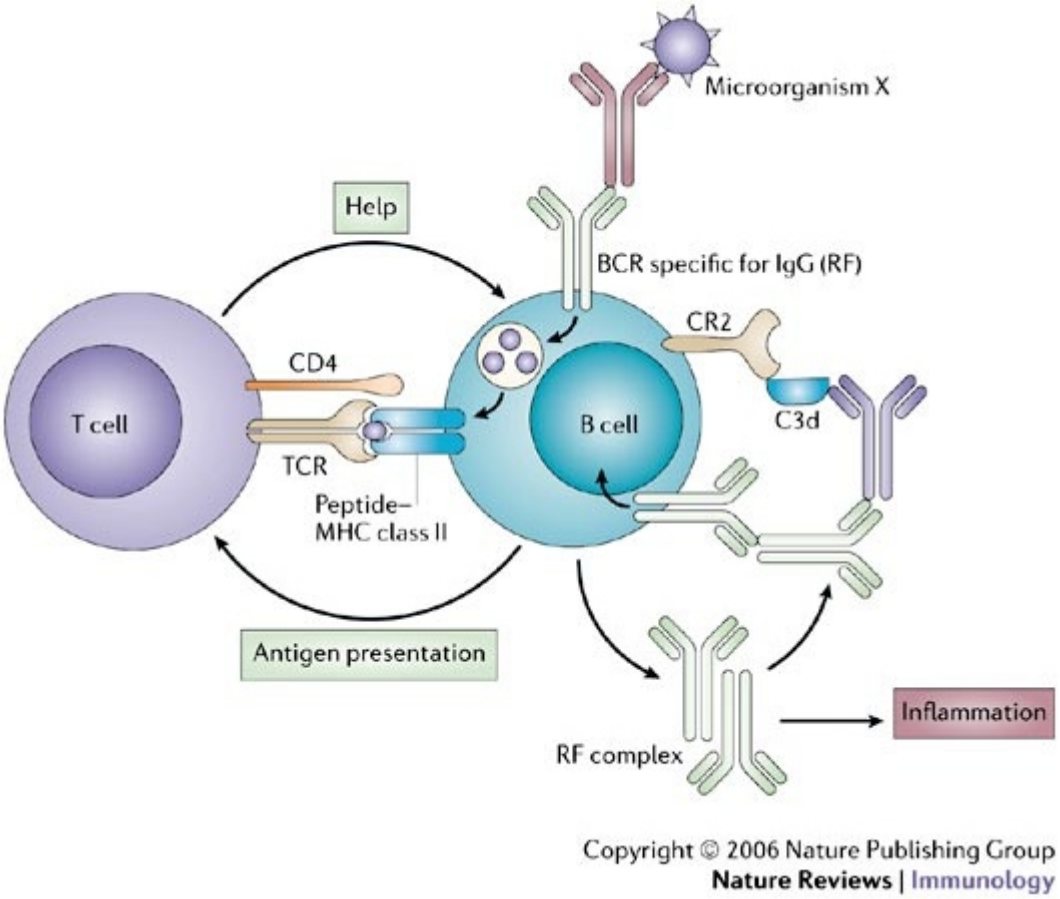


Model of the HC-B27 HLA-B27 heavy-chain homodimer

Antigen presentation and clonal expansion



A role for B cells?

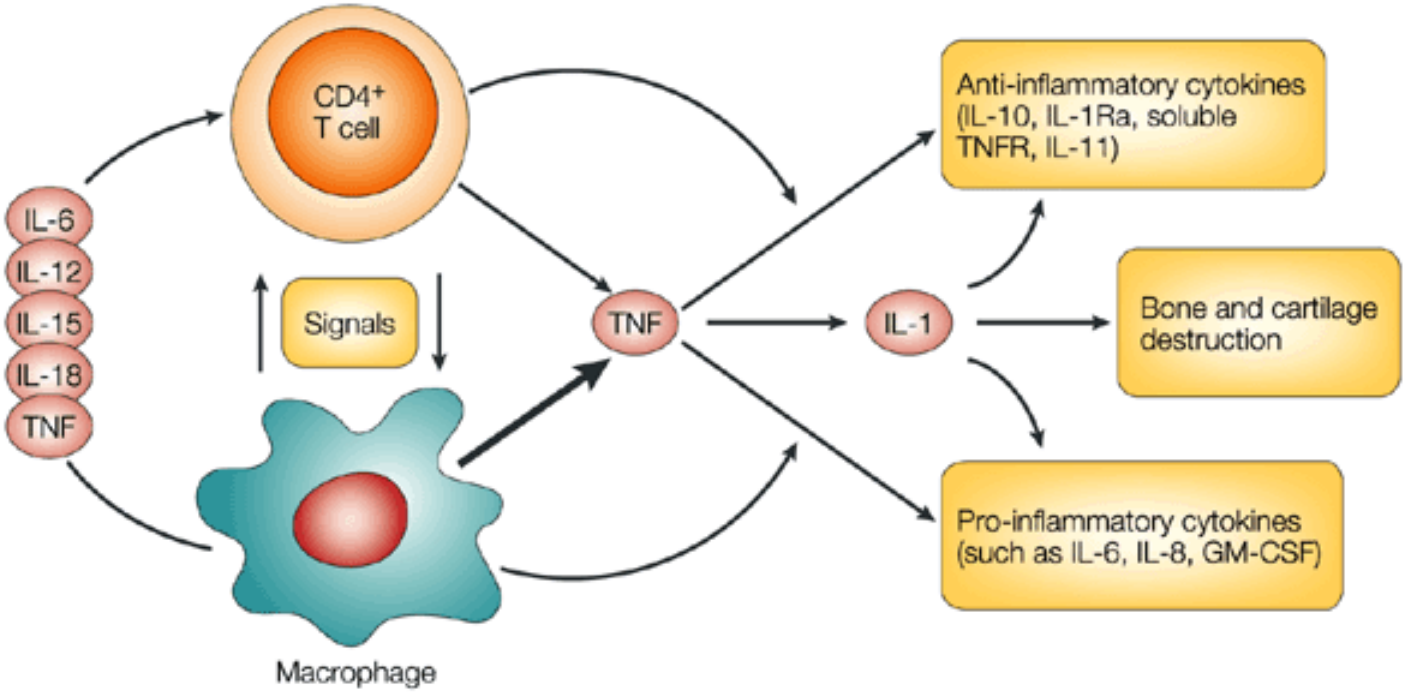


A role for B cells?

RPMS, Hammersmith Hospital

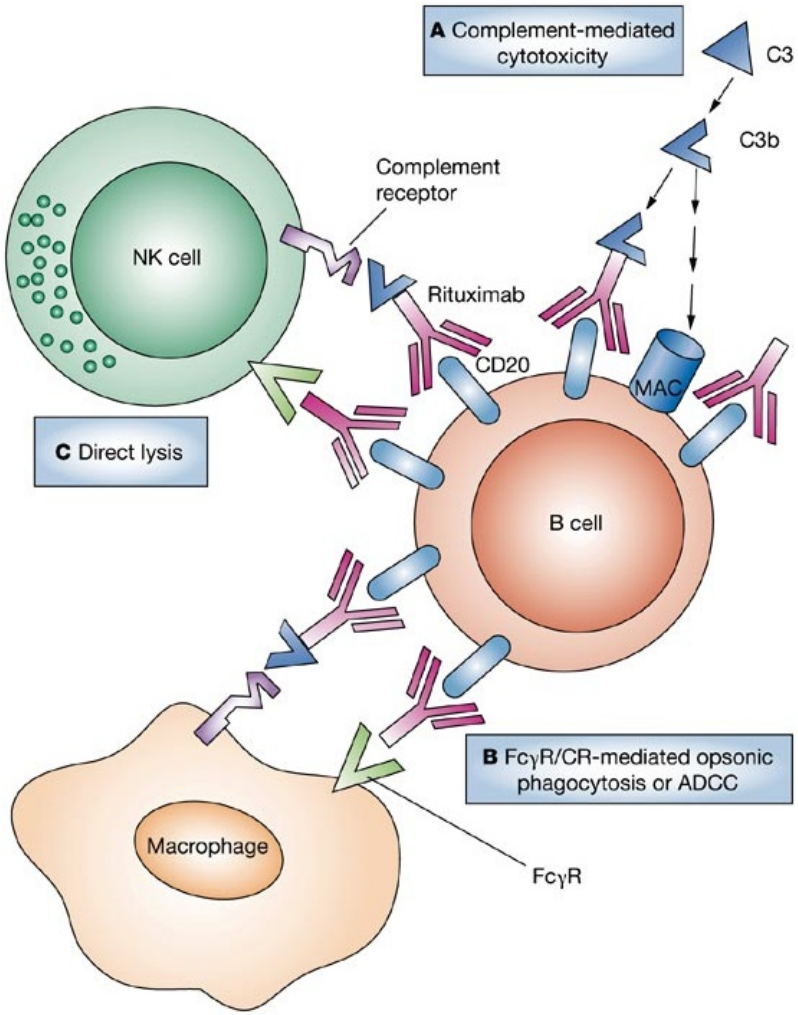
Feldman and Maini

A pivotal role for TNF in rheumatoid inflammation



Infliximab

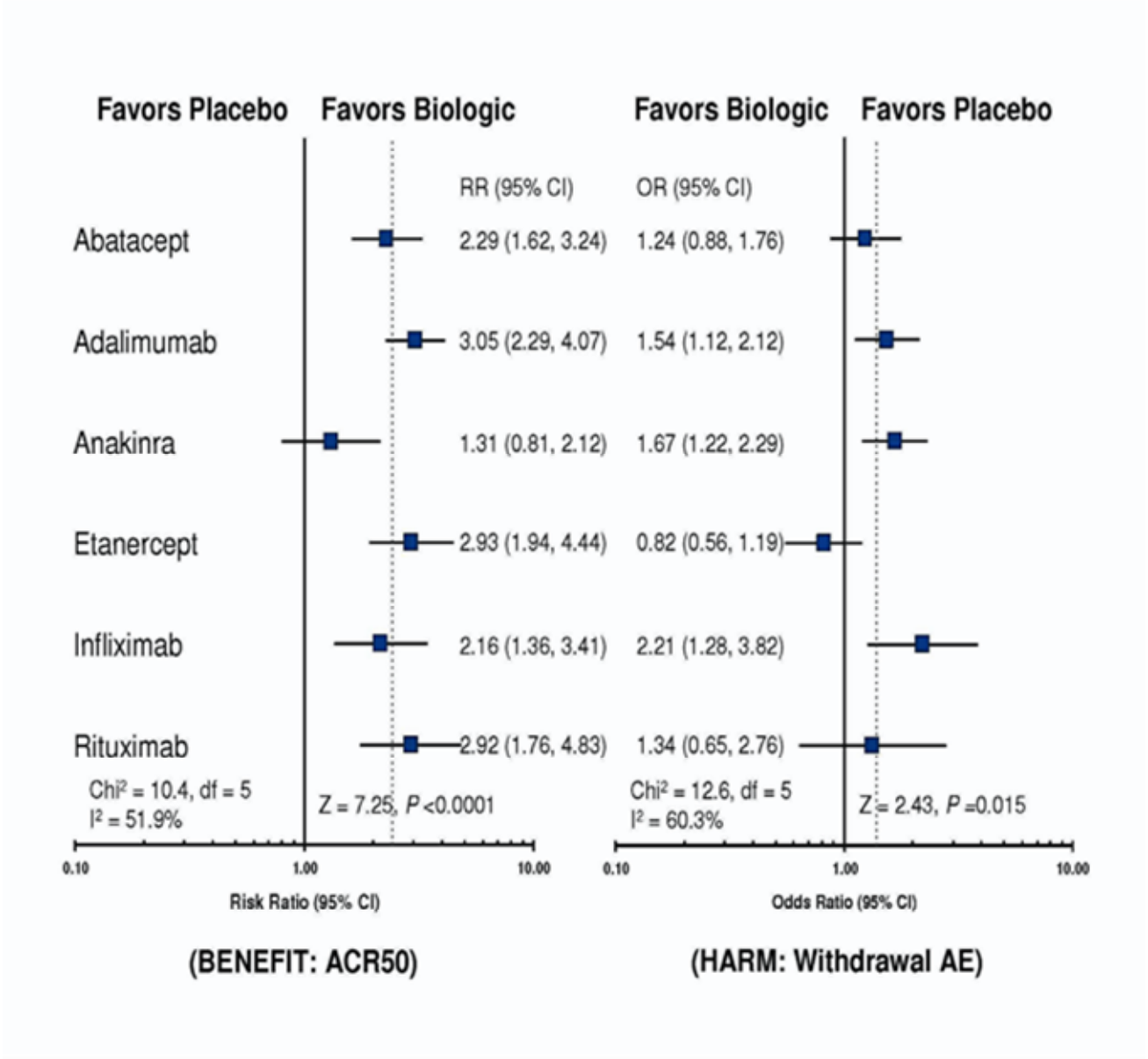
Anti-B cell therapy



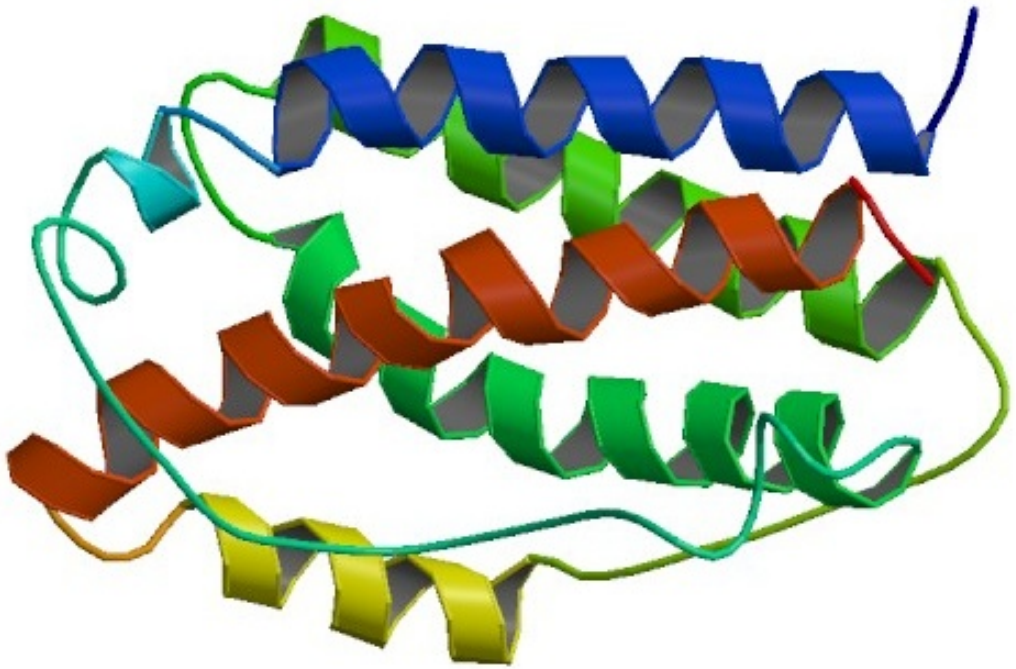
Biologics in RA

Generic name	Trade name	Target
Infliximab	Remicade	TNF
Etanercept	Enbrel	TNF
Adalimumab	Humira	TNF
Golimumab	Simponi	TNF
Rituximab	MabThera	CD20 (B Cells)
Anakinra	Kineret	IL-1
Abatacept	Orencia	CTLA-4 (costimulation)
Tocilizumab	Actrema	IL-6

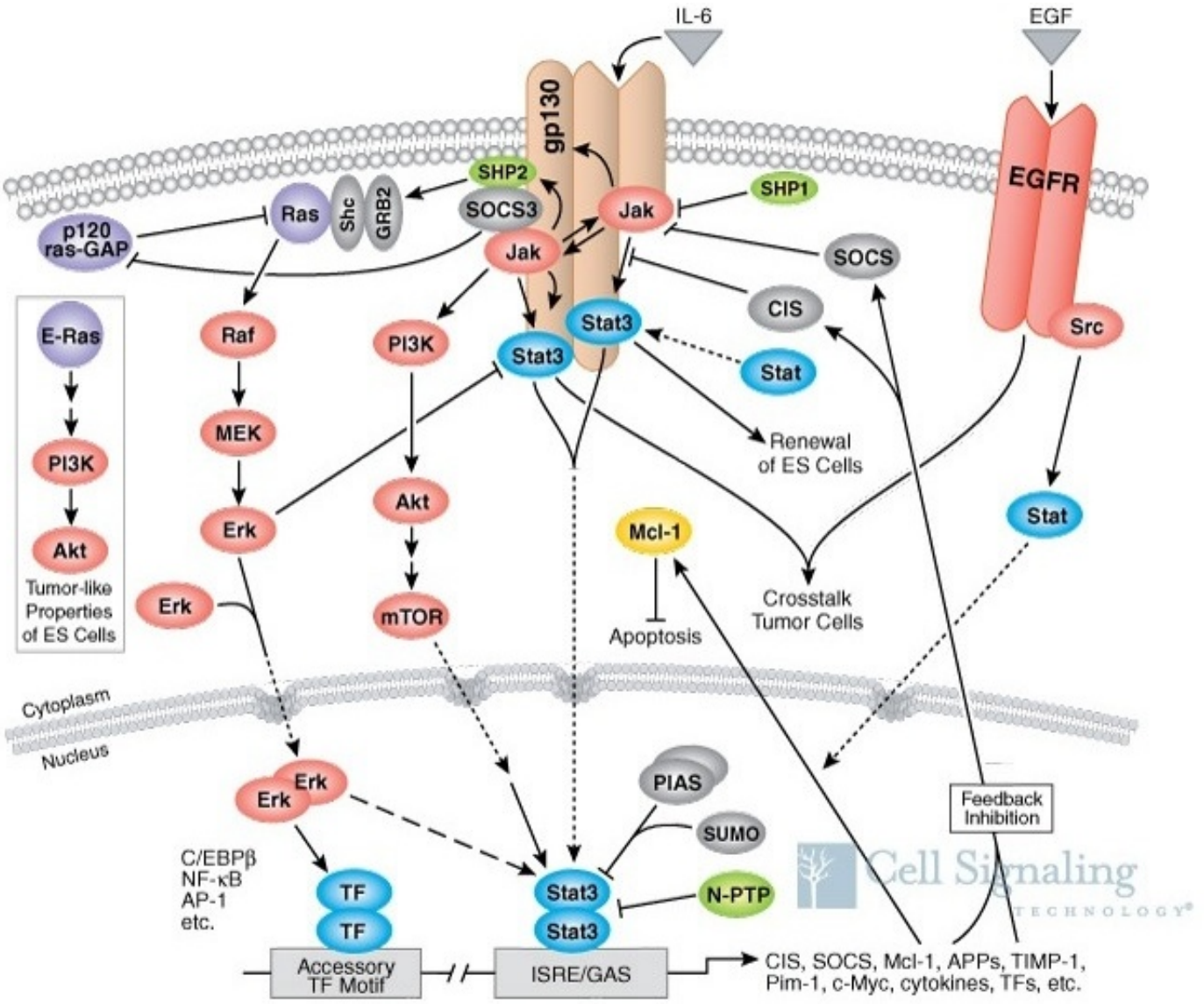
Cochrane review of Biologic DMARDs



IL-6



Signal transduction via the IL-6 Jak/Stat pathway



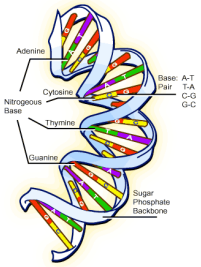
Other important developments in RA

Genetic markers

A new serological test

Cigarette smoking

Genetics of Rheumatoid Arthritis

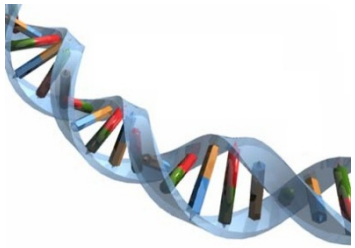


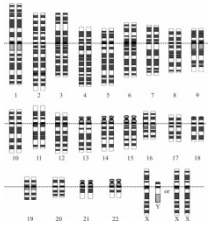
Prevalence
- ≈ 0.8% general population
- 5% affected sibling
- 25-30% with affected identical twin

Multigenic (>4 loci) based on family studies

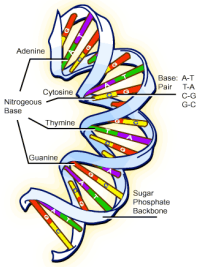
HLA explains ⅓ to ½ of genetic susceptibility

Strongest association is with “shared epitope” (QKRAA)
- in antigen binding groove
- homology with HSP
- HLA-DRB1*0101, *0401 etc
- Commonly found in HLA-DR4 and HLA-DR1





Genetics of Rheumatoid Arthritis



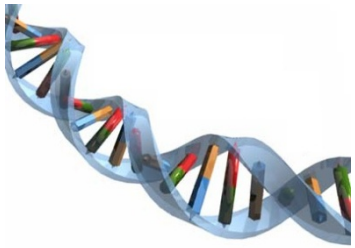
Other genes

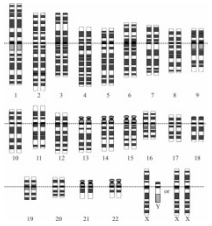
PTPN22

- •intracellular tyrosine kinase
- •negative regulator of T cell activation
- •OR for RA ≈ 2

PADI4

- •Peptidylarginine deiminase 4
- •converts arginine to citrulline
- •OR for RA ≈ 2 in Japanese (not replicated in Europeans)





Antibodies to cyclic citrullinated peptide in RA

	Sensitivity %	Specificity %
RF	75	74
Anti-CCP	68	96

Rheumatoid Arthritis and Tobacco Smoke

Cigarette smoke citrullinates peptides

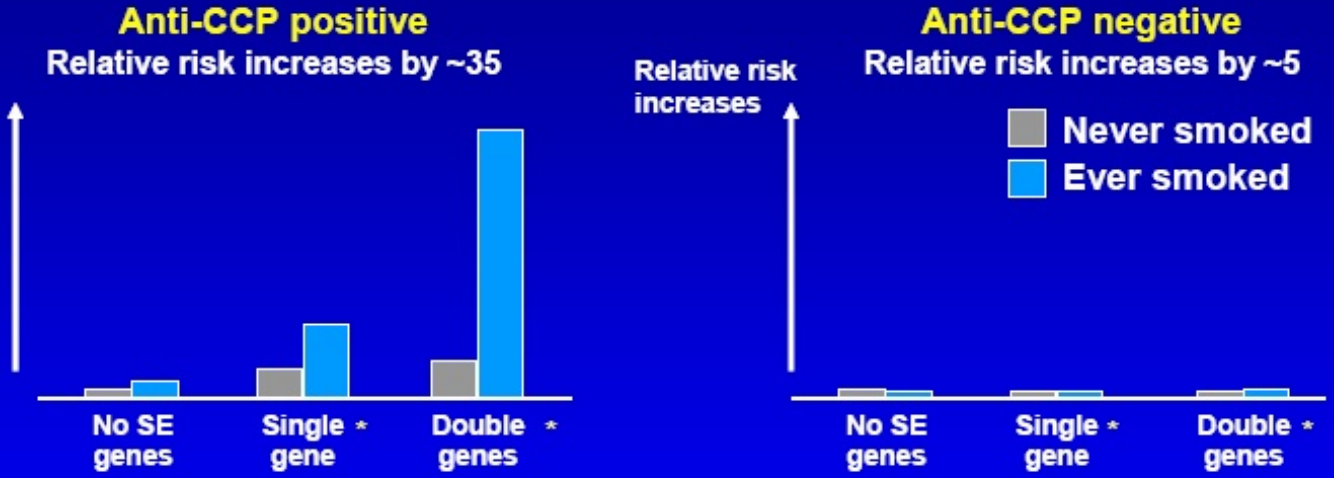
- Citrullinated peptides in BAL of smokers but not non-smokers

RA more common in smokers than in non-smokers

Antibodies to cyclic citrullinated peptide in RA

RA Susceptibility: Shared Epitope, Smoking, Anti-CCP Antibodies

Relative risk of rheumatoid arthritis in individuals with different combinations of smoking habits and SE genotype



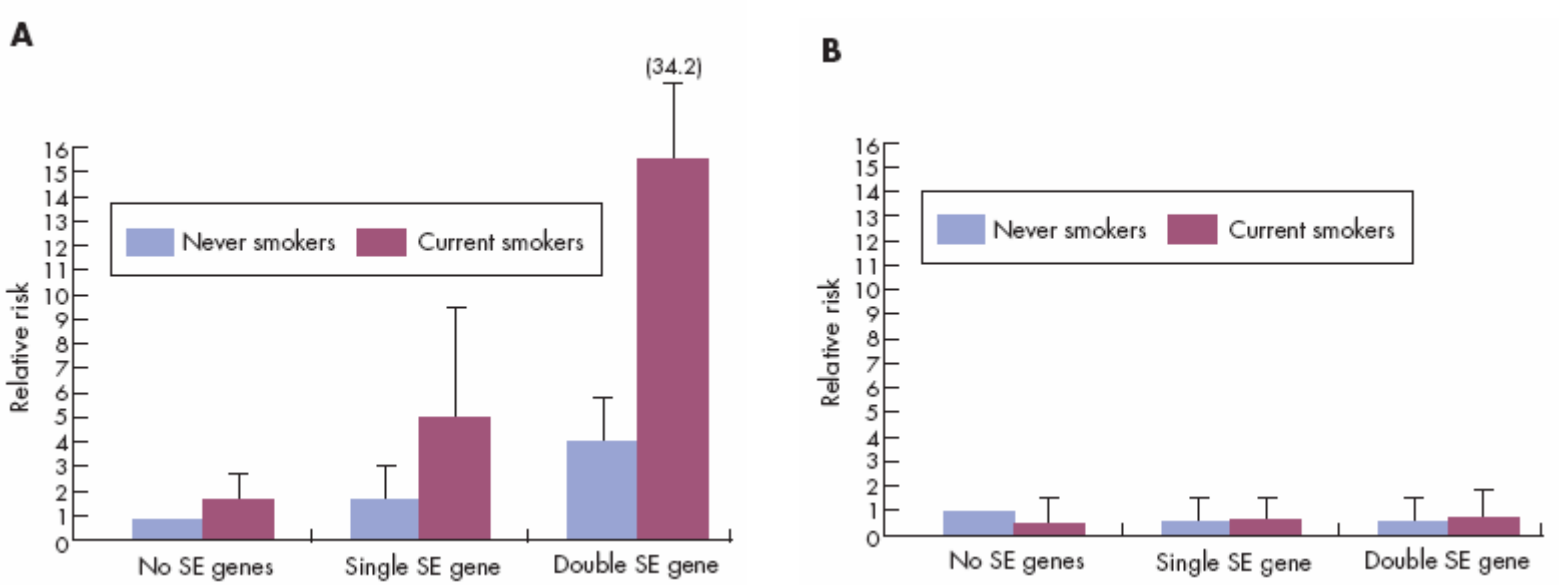
- 913 RA patients, 631 controls
- Dose-dependent association of smoking with anti-CCP in RA
- SE genes risk factor only for anti-CCP positive RA
- Smoking and SE synergistically increase risk for anti-CCP + RA

* Single gene = heterozygous, double genes = homozygous for shared epitope

Klareskog K, *et al*. EULAR 2005, #THU0190

Rheumatoid factor in RA

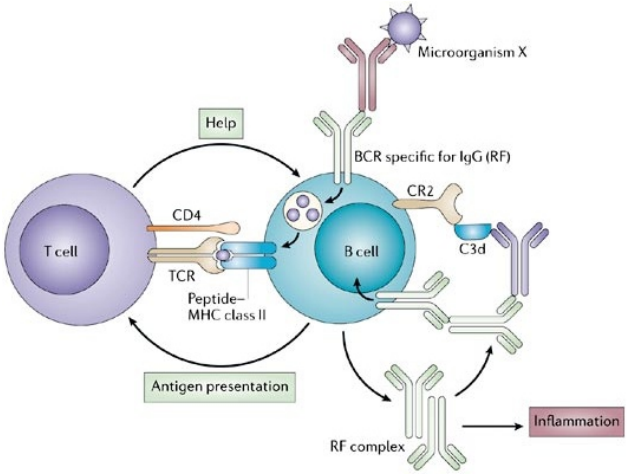
Influence of smoking on risk of RA in (A) RF+ and (B) RF- cases

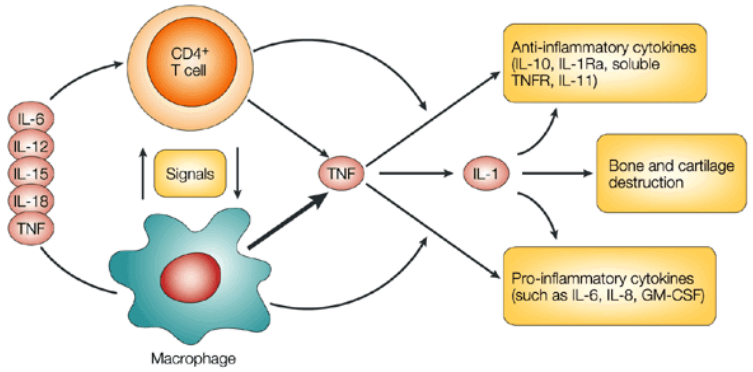


Rheumatoid Arthritis and Tobacco Smoke

Hypothesis:

- Cigarette smoke causes deimination of R by PADI
- Citrullinated peptides are formed
- Shared epitope presents these neoantigens
- Immunological tolerance is broken
- Autoimmune response in joints and other tissues





The evidence from paleopathology

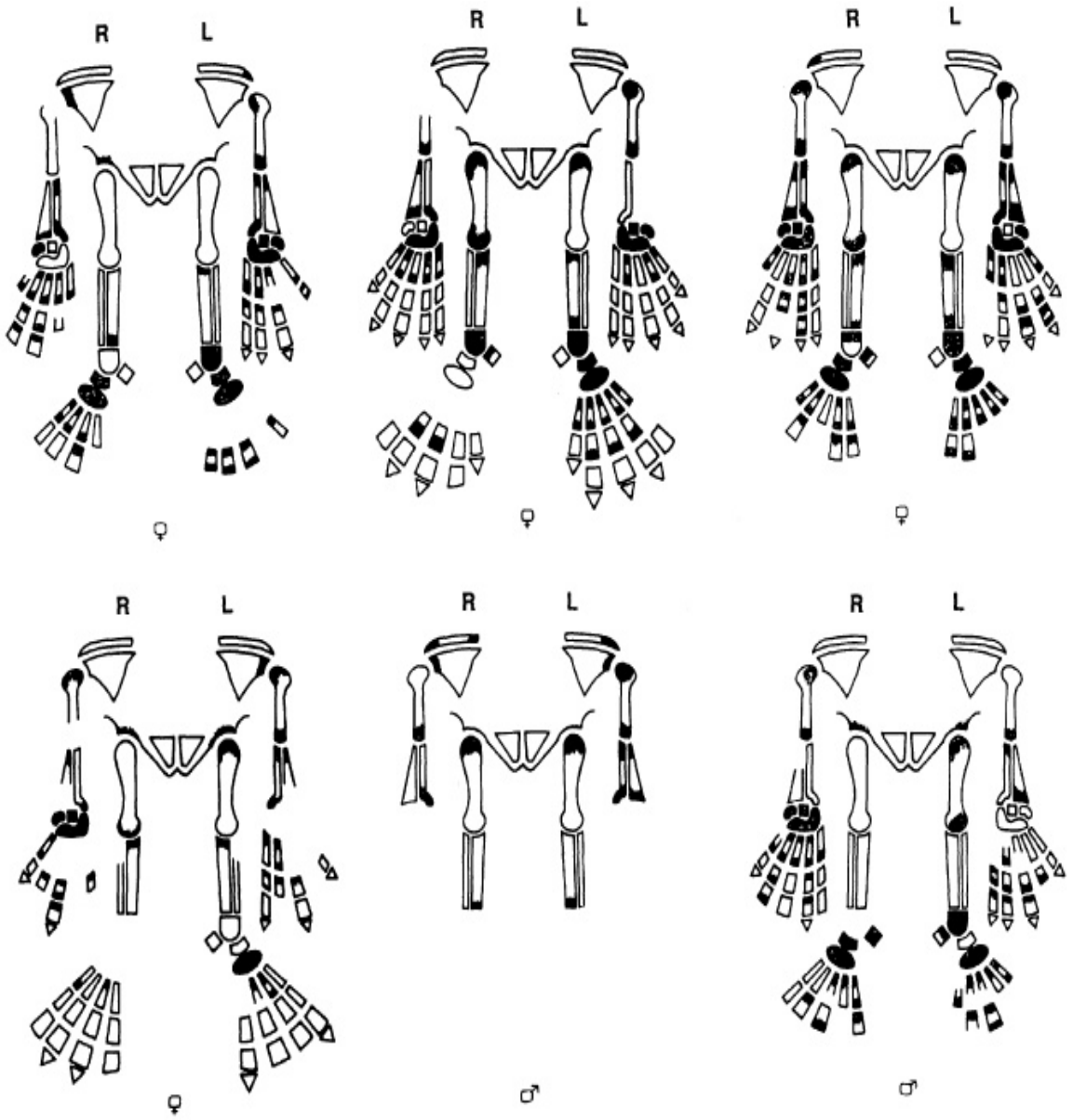
Rheumatoid Arthritis

First description in Old World 1800 Landre-Beauvais

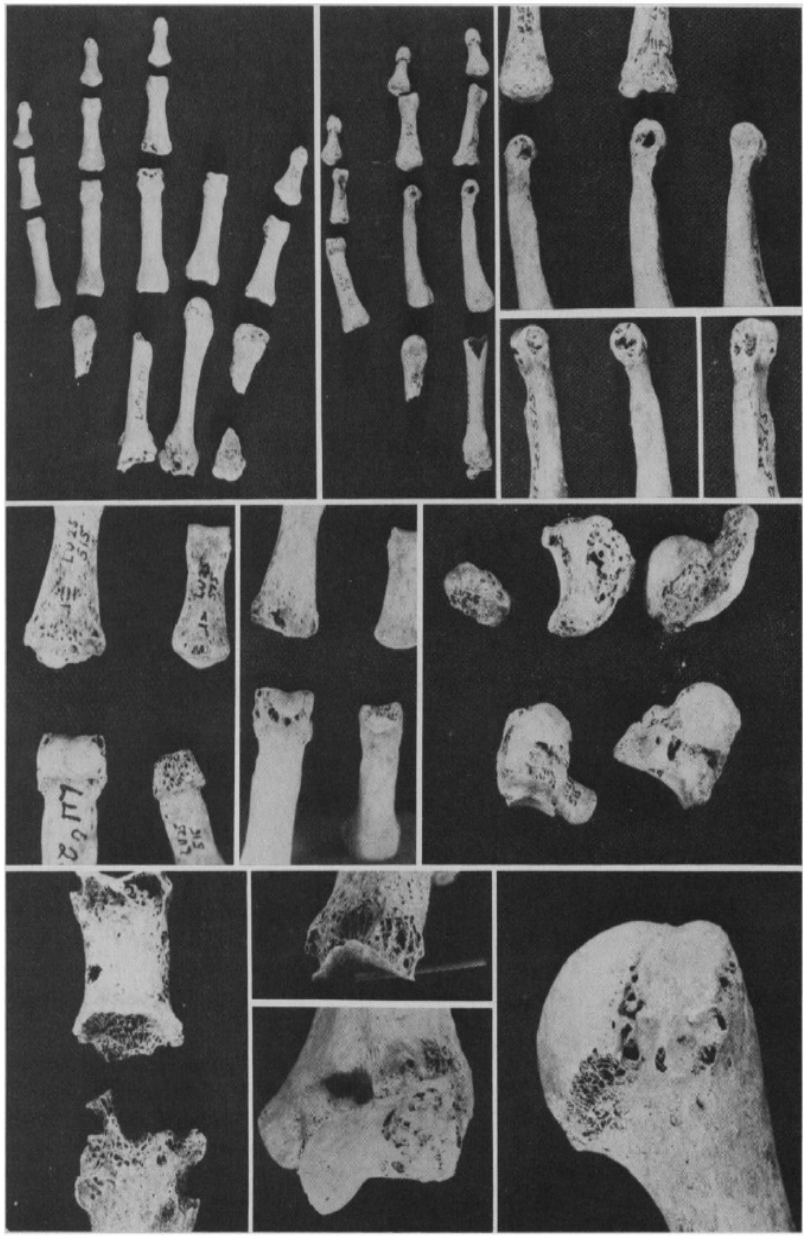
RA not seen in pre-C19 European skeletal remains

Description of RA in 3000 to 5000 year old skeletons in NW Alabama

The evidence from paleopathology



The evidence from paleopathology



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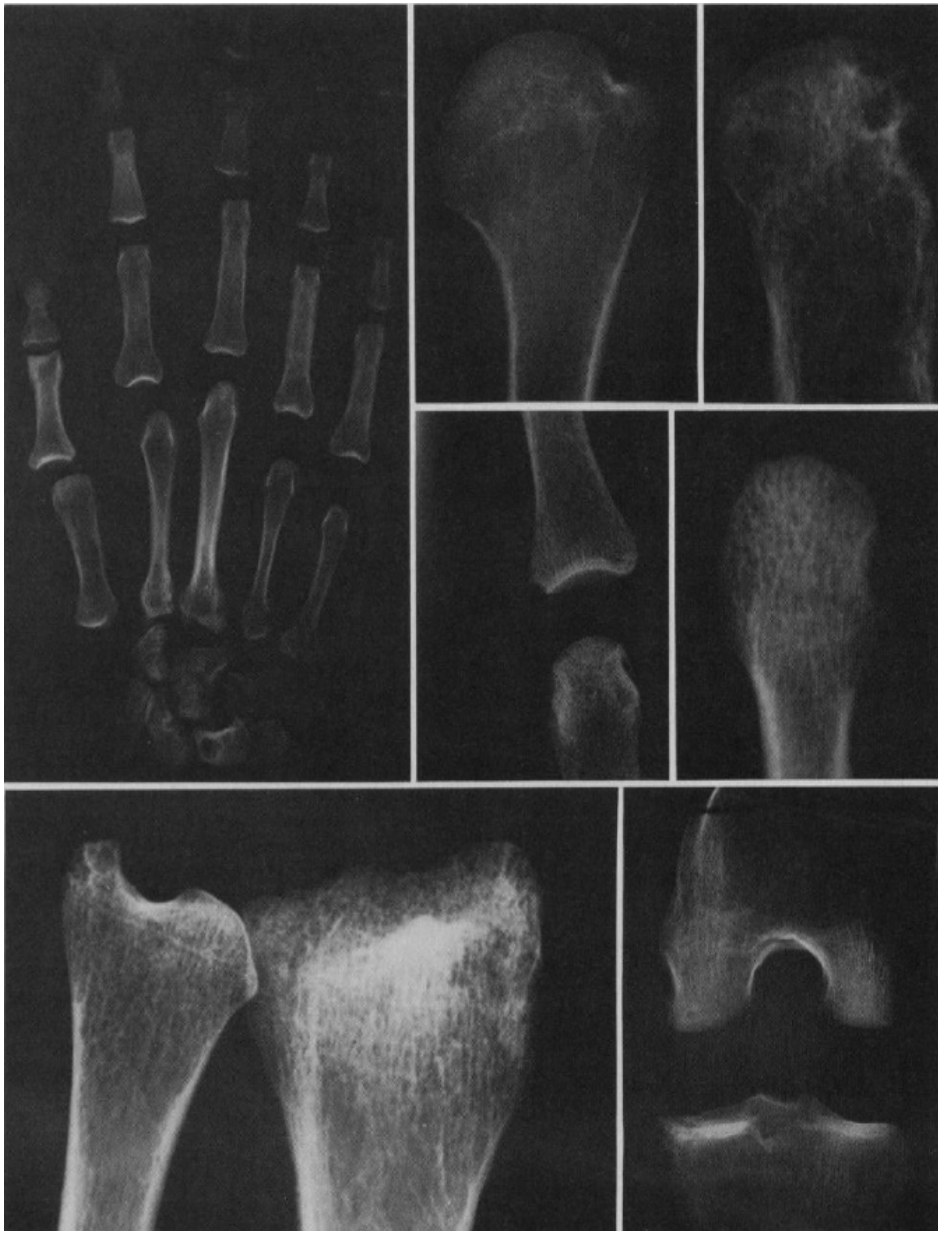
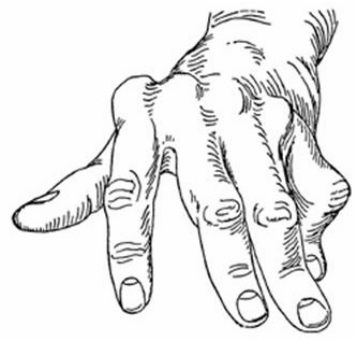
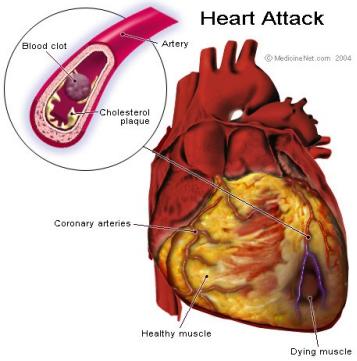


The evidence from paleopathology

The appearance of RA in the Old World may have been due to an environmental factor imported from North America

From wax to JAKs: Two decades of advances in rheumatology





Advances in measurement

Science is measurement

Measures of disease activity

- DAS28
- HAQ

Measures of outcome

- X-ray scoring of erosions
- HAQ

Measures of remission

Advances in measurement – DAS28

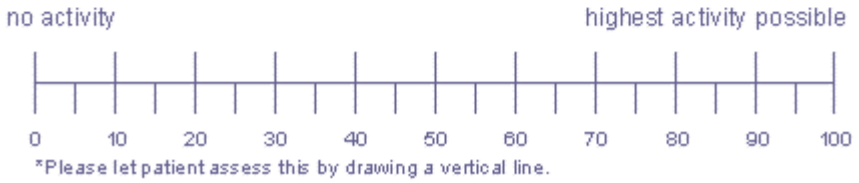
DAS28 inputs

❶ **Joint Count TEN28** ___|___

❷ **Joint Count SW28** ___|___

❸ **ESR** (after 1 hour in mm) ___|___|___

❹ **General Health** or patient's global assessment of disease activity
How active has your rheumatoid arthritis been during the last 7 days?*



*Please let patient assess this by drawing a vertical line.

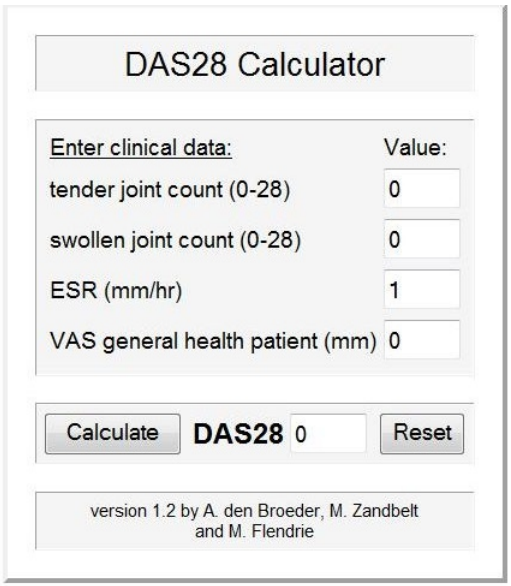
Advances in measurement – DAS28

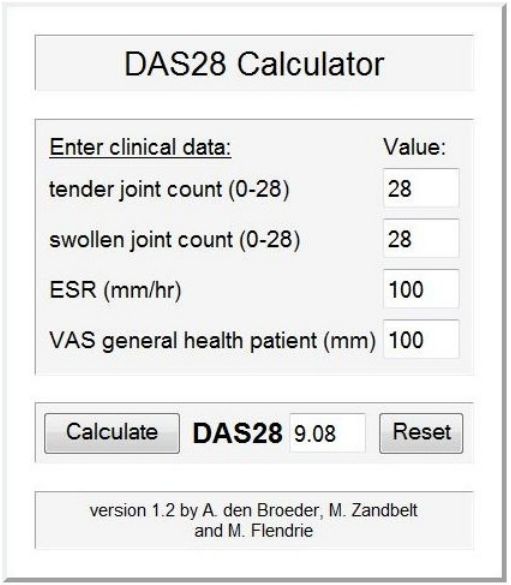
DAS28 formula

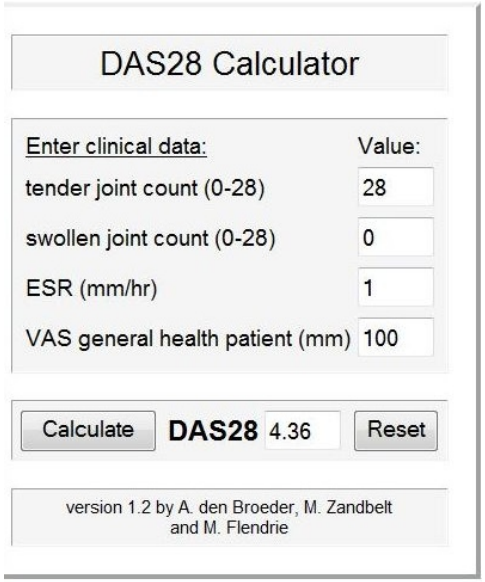
Formulas for DAS 28 calculation

$$0{,}56 \times \sqrt{\text{❶ TEN28}} + 0{,}28 \times \sqrt{\text{❷ SW28}} + 0{,}70 \times \ln(\text{❸ ESR (after 1 hour in mm)}) + 0{,}014 \times (\text{❹ Patient's assessment in mm}) = \text{DAS 28}$$

Advances in measurement – DAS28







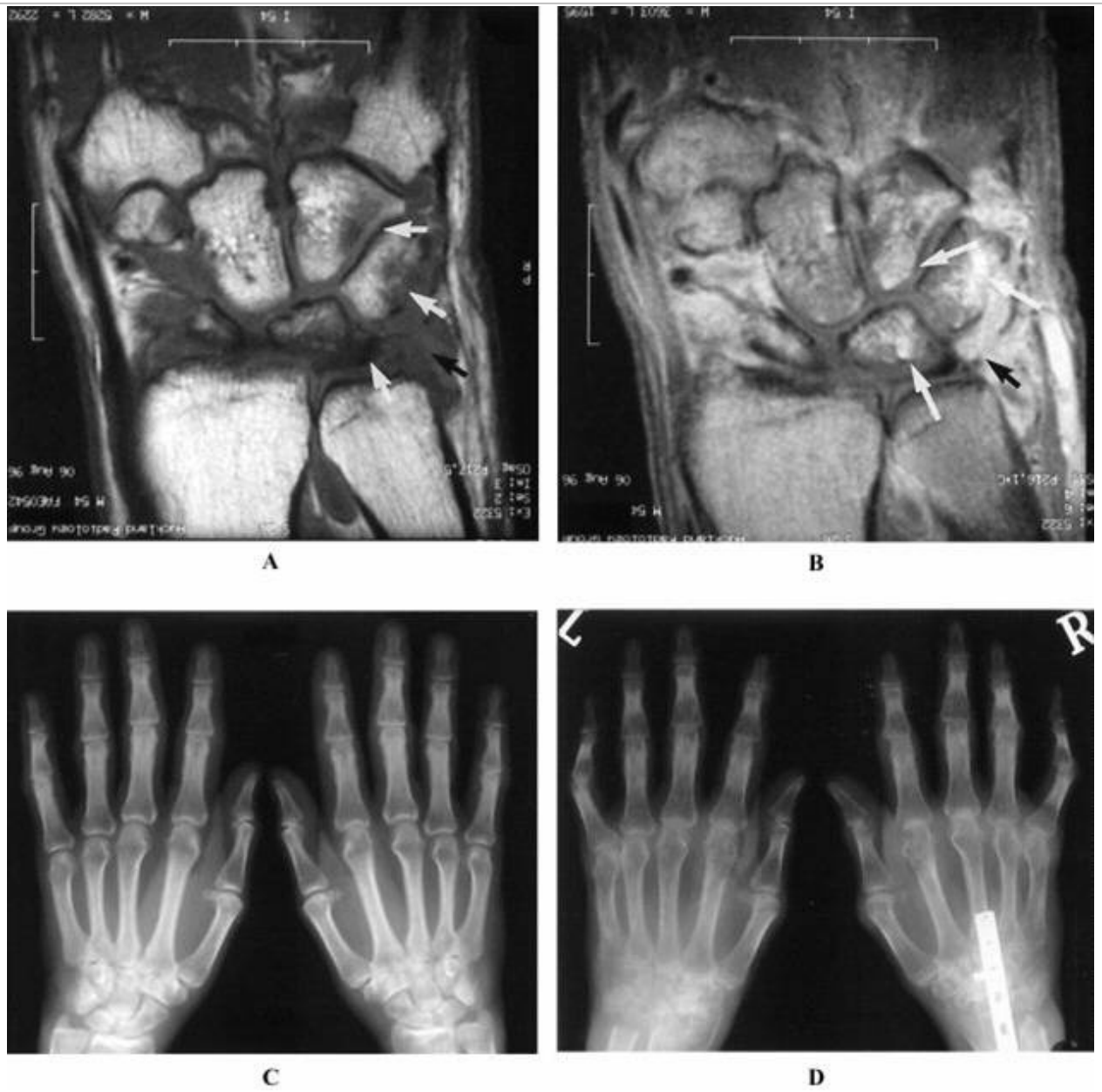
Current DAS28		DAS 28: Difference from initial value		
		>1.2	**>0.6 and ≤1.2**	**≤0.6**
≤3.2	Inactive	Good improvement	Moderate improvement	No improvement
>3.2 and ≤5.1	Moderate	Moderate improvement	Moderate improvement	No improvement
>5.1	Very active	Moderate improvement	No improvement	No improvement

Advances in measurement – HAQ

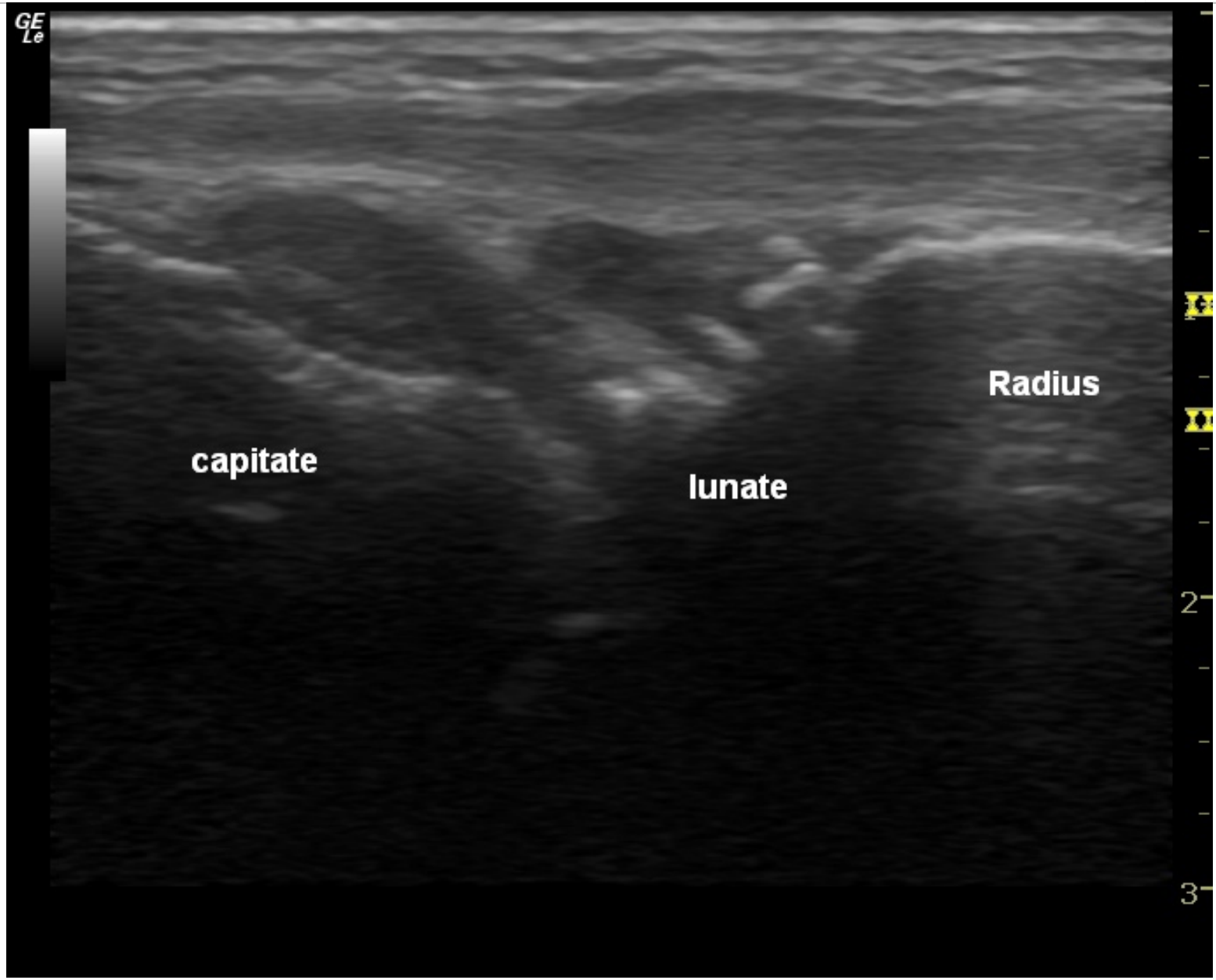
Place an X in the box which best describes your usual abilities *over the past week.*
Are you able to:

HAQ-II	Without any difficulty (0)	With some difficulty (1)	With much difficulty (2)	Unable (3)
Get on and off the toilet?				
Open car doors?				
Stand up from a straight chair?				
Walk outdoors on flat ground?				
Wait in a line for 15 minutes?				
Reach and get down a 5-pound object (e.g. bag of sugar) from just above your head?				
Go up 2 or more flights of stairs?				
Do outside work (such as yard work)?				
Lift heavy objects?				
Move heavy objects?				

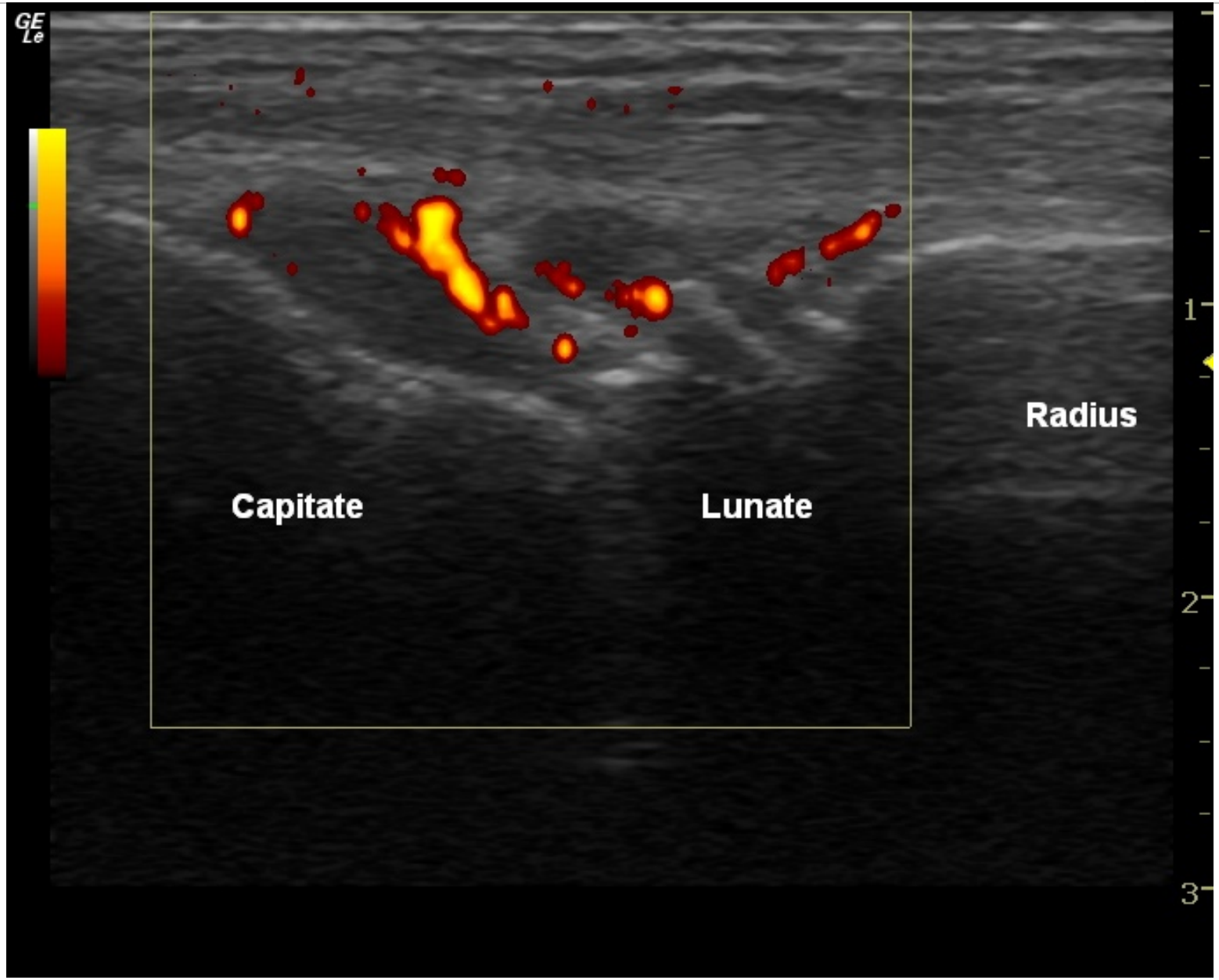
Advances in measurement – radiology



Advances in measurement – radiology



Advances in measurement – radiology



The early treatment imperative

Rationale of early Rx
1)Erosive process starts at onset
2)Damage correlates with AUC of inflammation v time
3)Subclinical disease may cause damage
4)Early Rx may modify immune response

COBRA study

Boers M et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *The Lancet; Aug 2, 1997; 350, 9074;*

The early treatment imperative

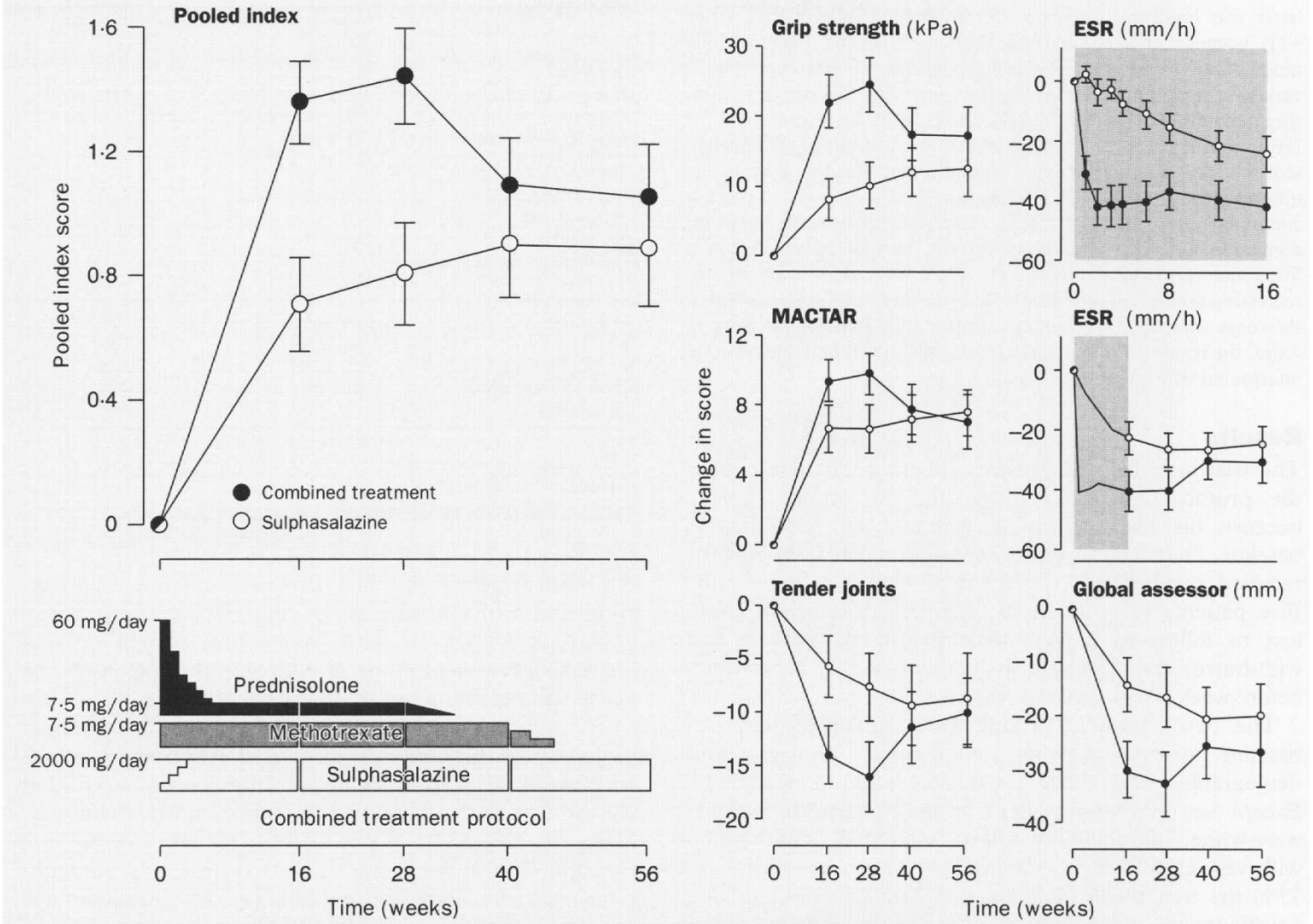


Figure 2: **Clinical outcomes of treatment, expressed as mean (95% CI) pooled index and changes in its component parts**
Positive values indicate improvement in pooled index, grip strength, and MACTAR (McMaster Toronto arthritis) questionnaire. Negative values indicate improvement in the remaining measures. Changes in ESR in first 16 weeks are shown in graph in upper right corner (note different time scale).

The early treatment imperative

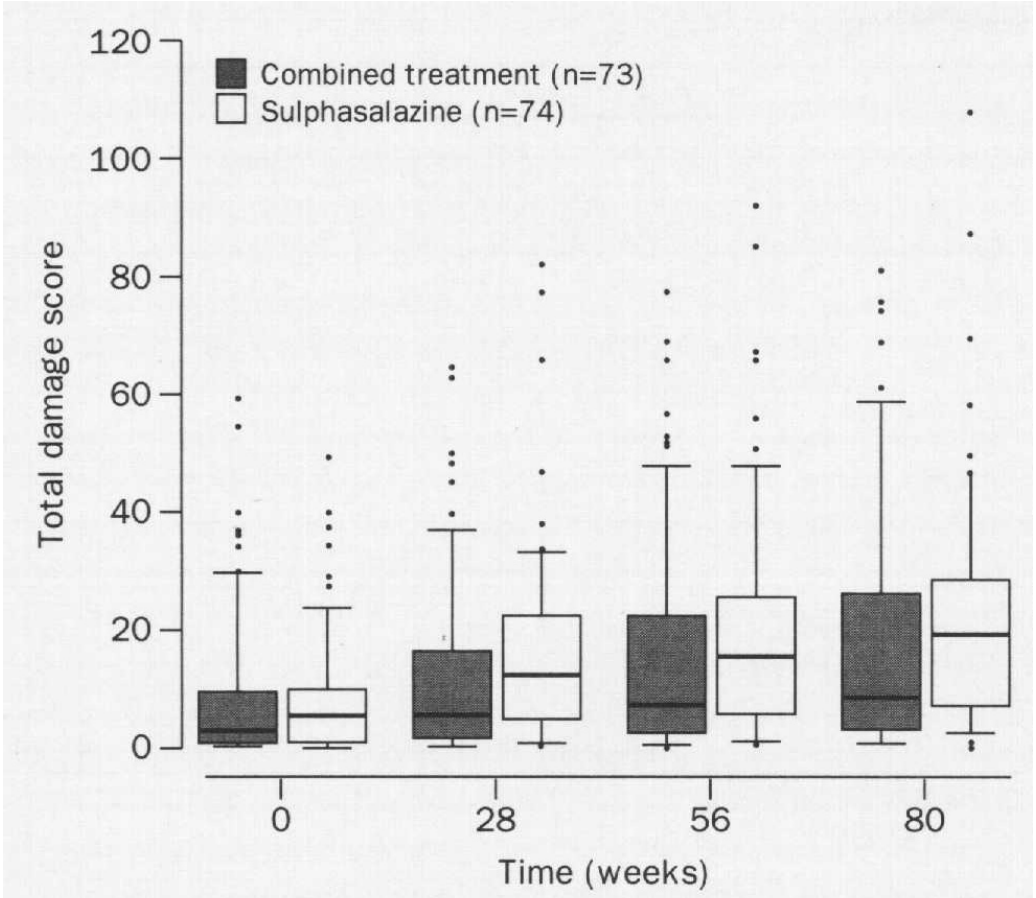
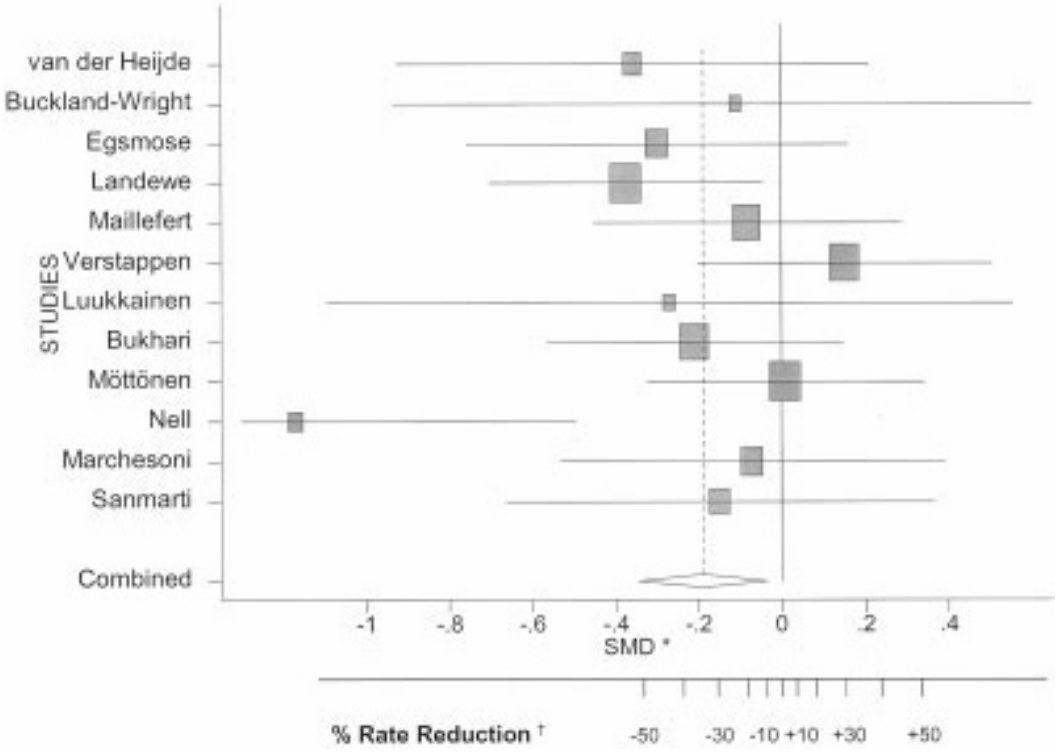


Figure 3: **Effect of treatment on total radiographic damage score**

Box-whisker plots of absolute radiographic damage scores (Sharp van der Heijde method; summed total scores for erosions and joint-space narrowing in hands and feet). Horizontal line in box=median; limits of box=25th and 75th percentiles; whiskers=10th and 90th percentiles; values above and below these plotted separately.

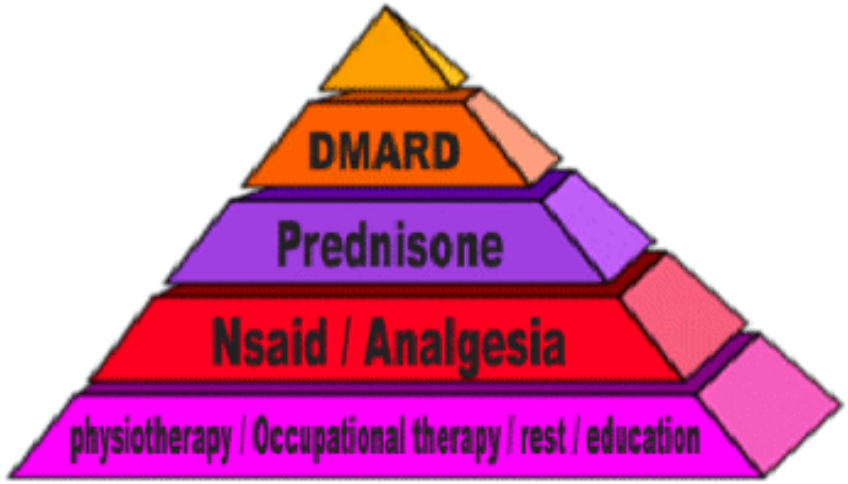
The early treatment imperative

Statistical evidence for a sustained effect of early treatment intervention on long-term joint damage.



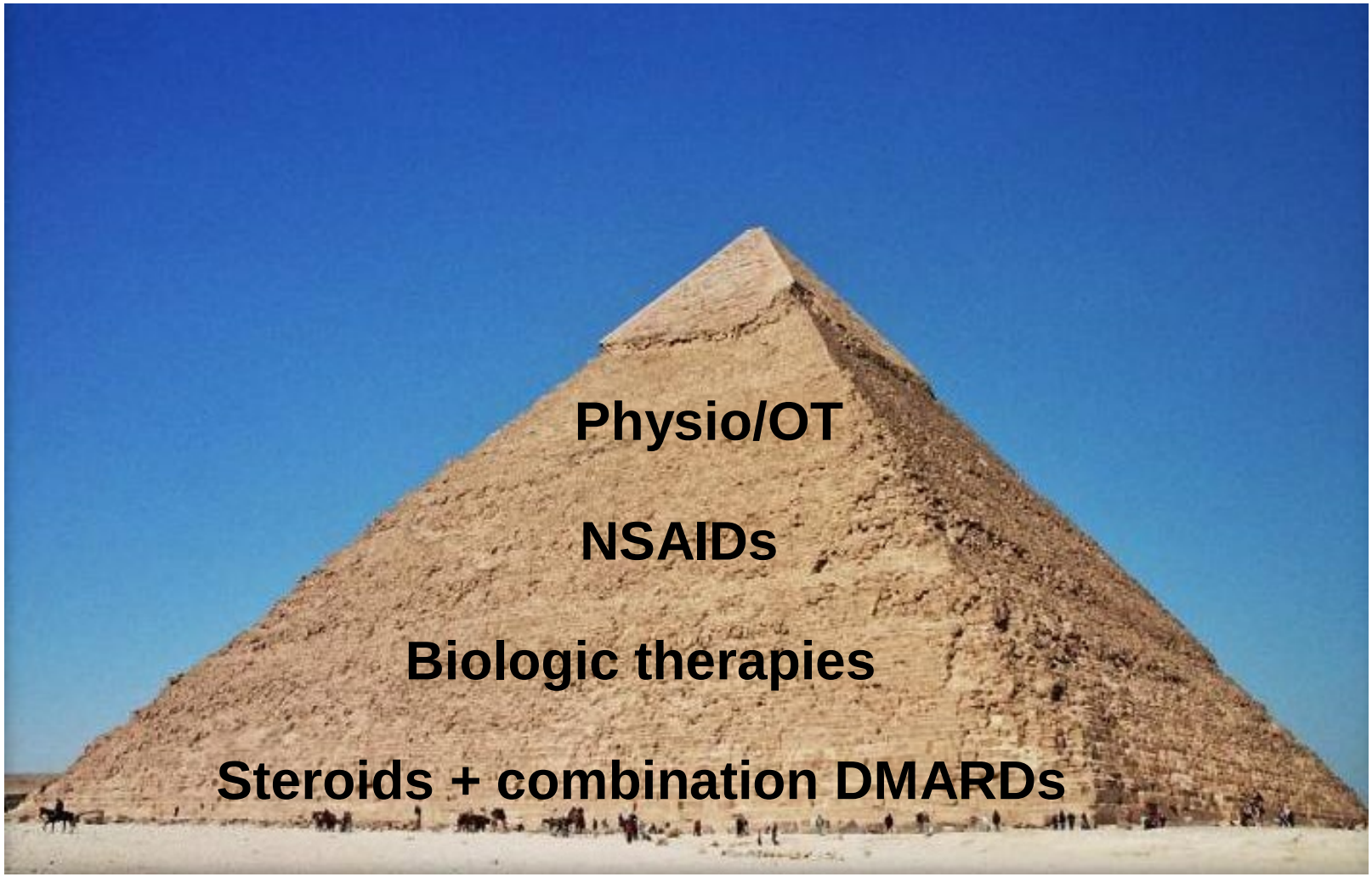
Axel Finck et al. Arthritis & Rheumatism (Arthritis Care & Research) Vol. 55, No. 6, December 15, 2006, pp 864–872

Inverting the pyramid

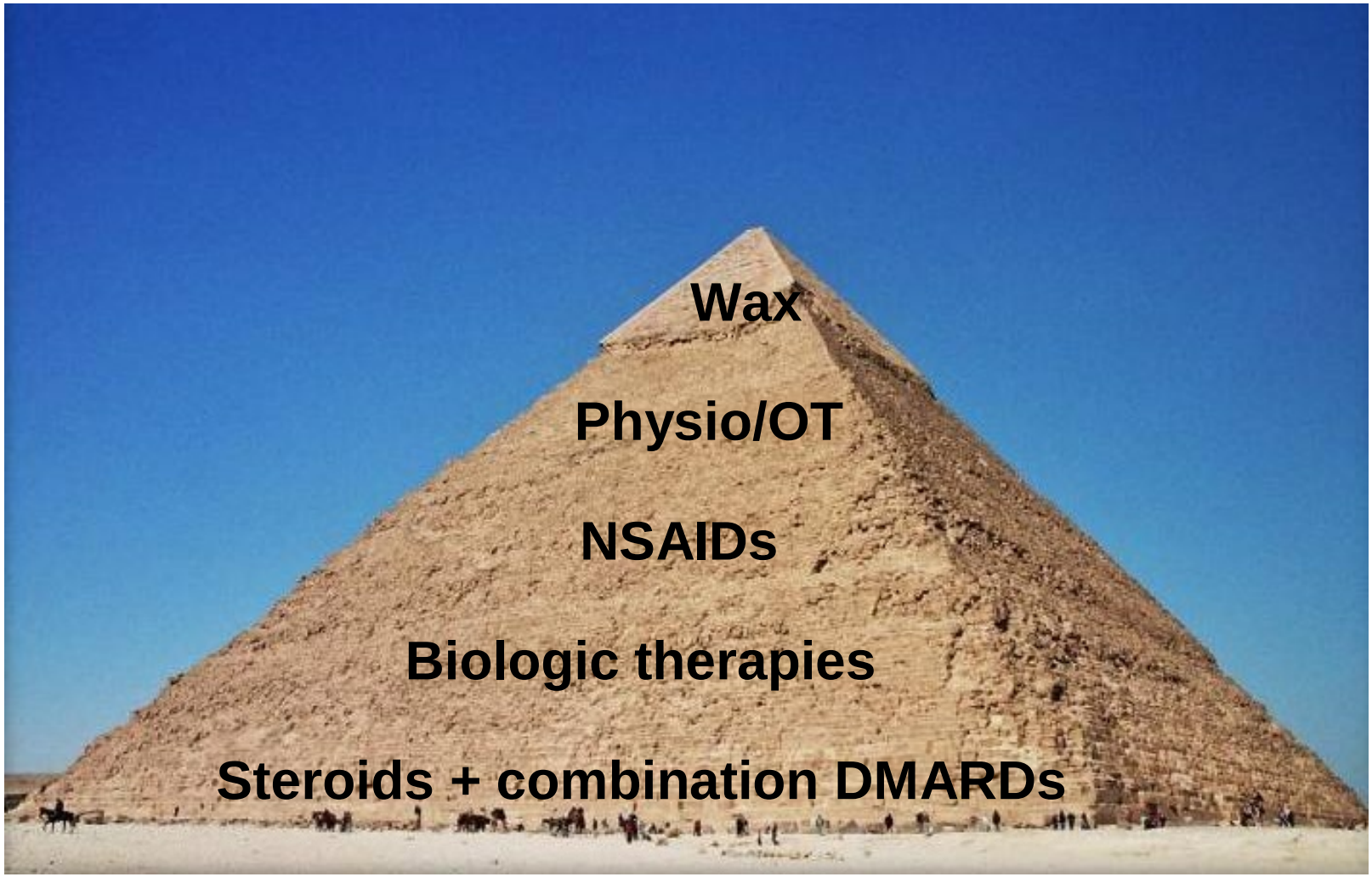


Inverting the pyramid

The treatment pyramid revisited



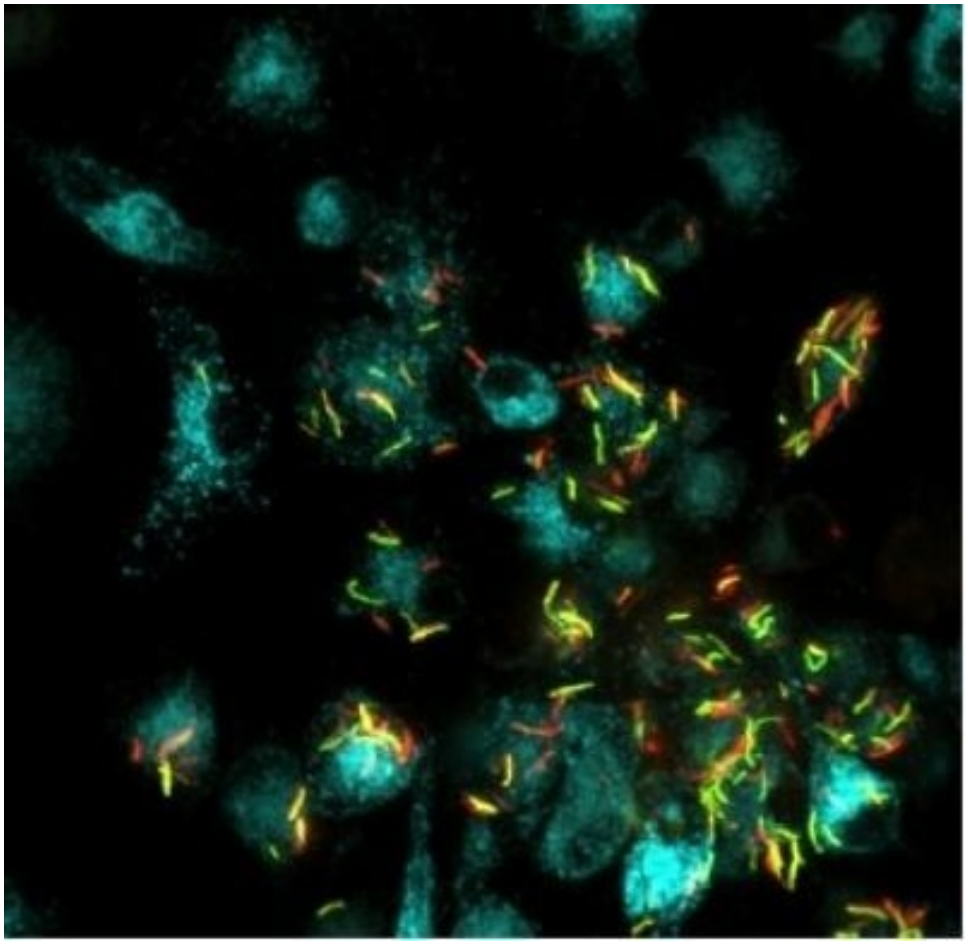
The treatment pyramid revisited



Safety issues

Safety of undertreated disease
Immuno-suppression
    steroids>bDMARDs>DMARDs
Life expectancy
    MTX
Awareness of specific issues
    MTX lung
    Reactivation of latent TB

Reactivation of latent TB



Summary

Approach to treatment has changed in the last 2 decades

New treatments and new strategies minimise damage

Smoking increases risk of RA

RA increases risk of cardiovascular disease

RA can be diagnosed earlier

Early treatment improves outcome

Summary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I NEED YOU TO TAKE THESE PILLS BECAUSE THE PHARMACEUTICAL REP IS SMOKING HOT.
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