What has happened to Rheumatoid Arthritis in the last 40 years?

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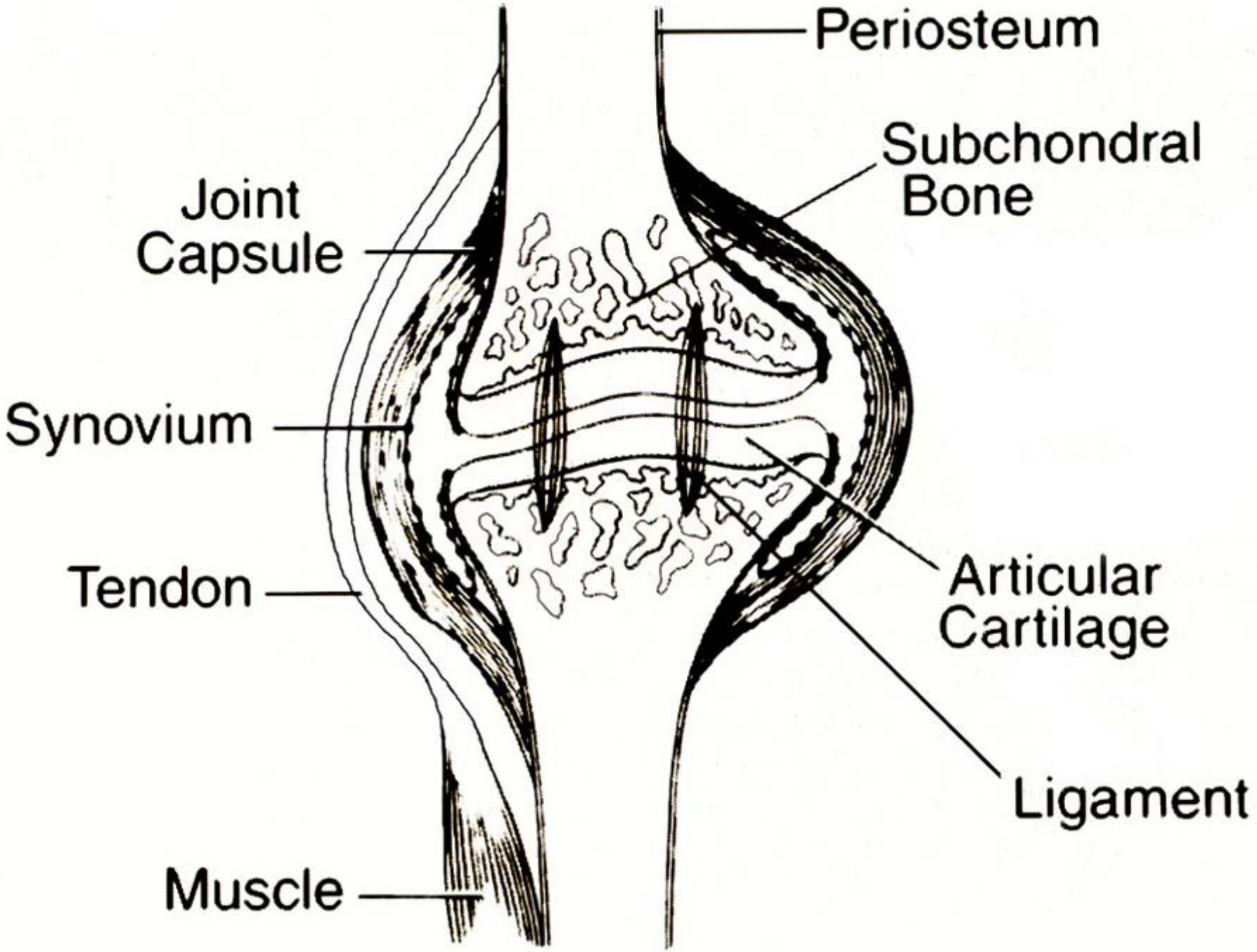
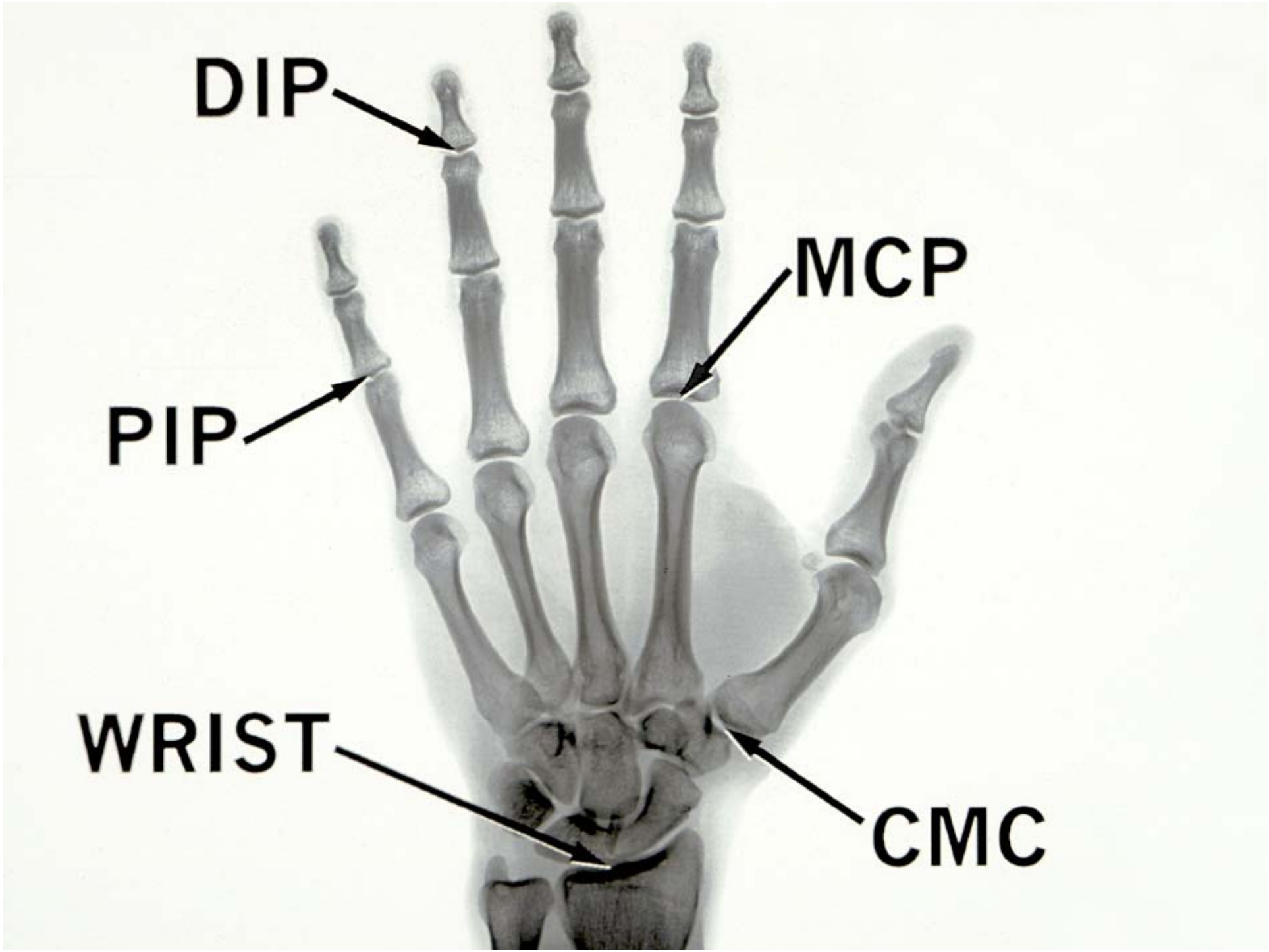

Periosteum
Subchondral Bone
Joint Capsule
Synovium
Tendon
Articular Cartilage
Ligament
Muscle


DIP
MCP
PIP
WRIST
CMC

Rheumatoid Arthritis in 1975

Moderate RA with Dramatic Synovitis

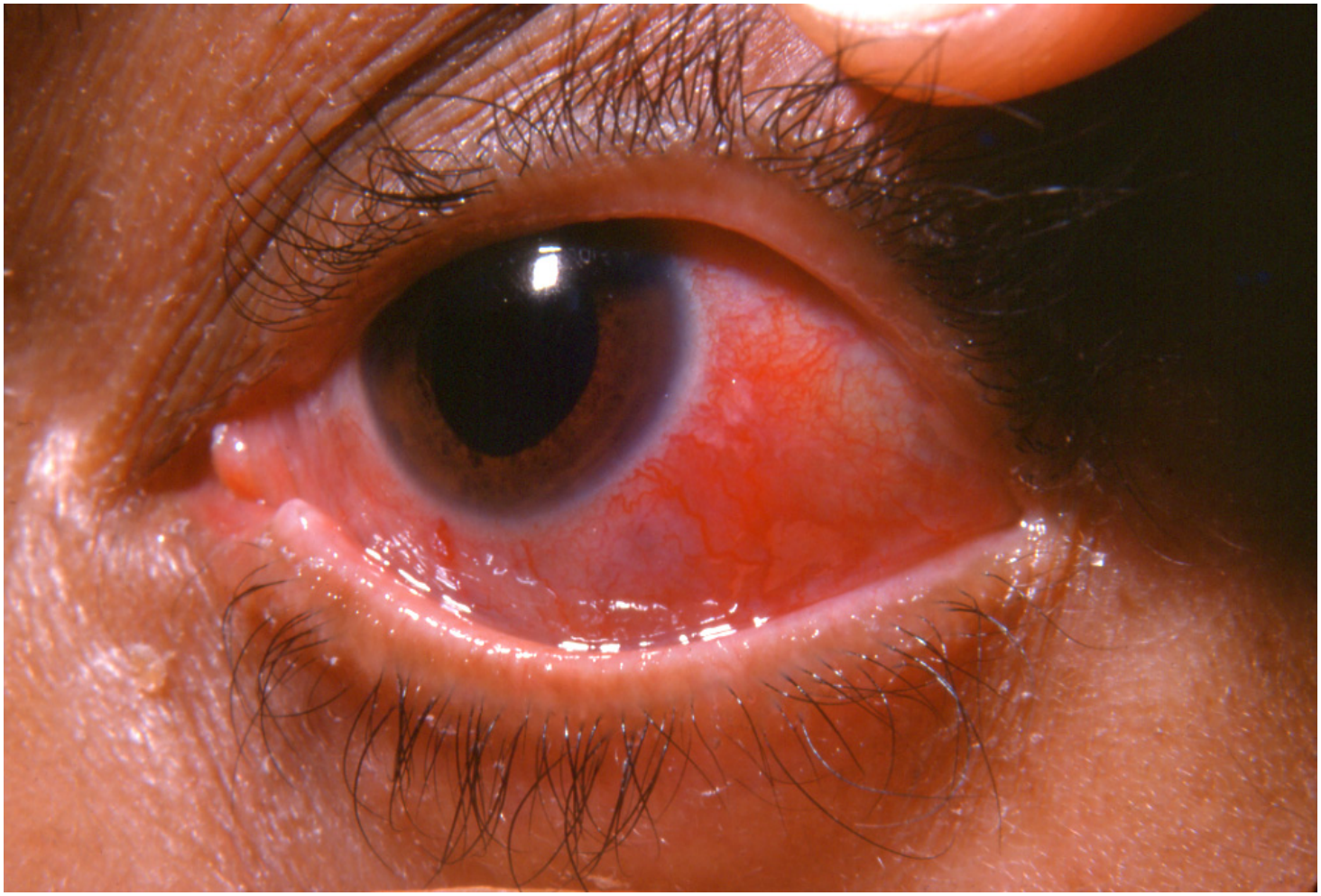
Progressive RA with MCP and Wrist Disease

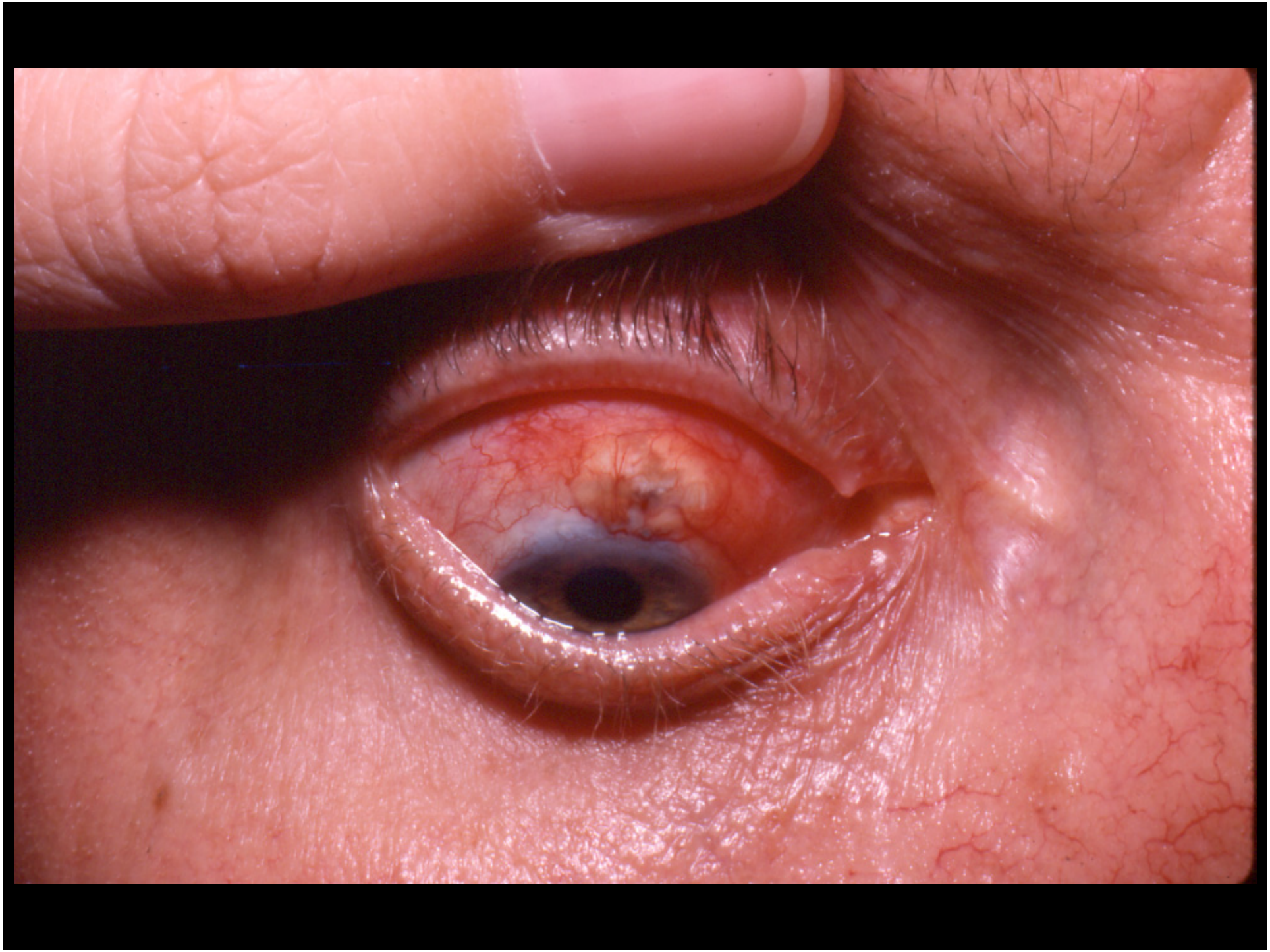
Late RA with Early Deformities and Nodules

Late RA with Nodules and Deformities

Late RA with Severe Deformities

Episcleritis RA



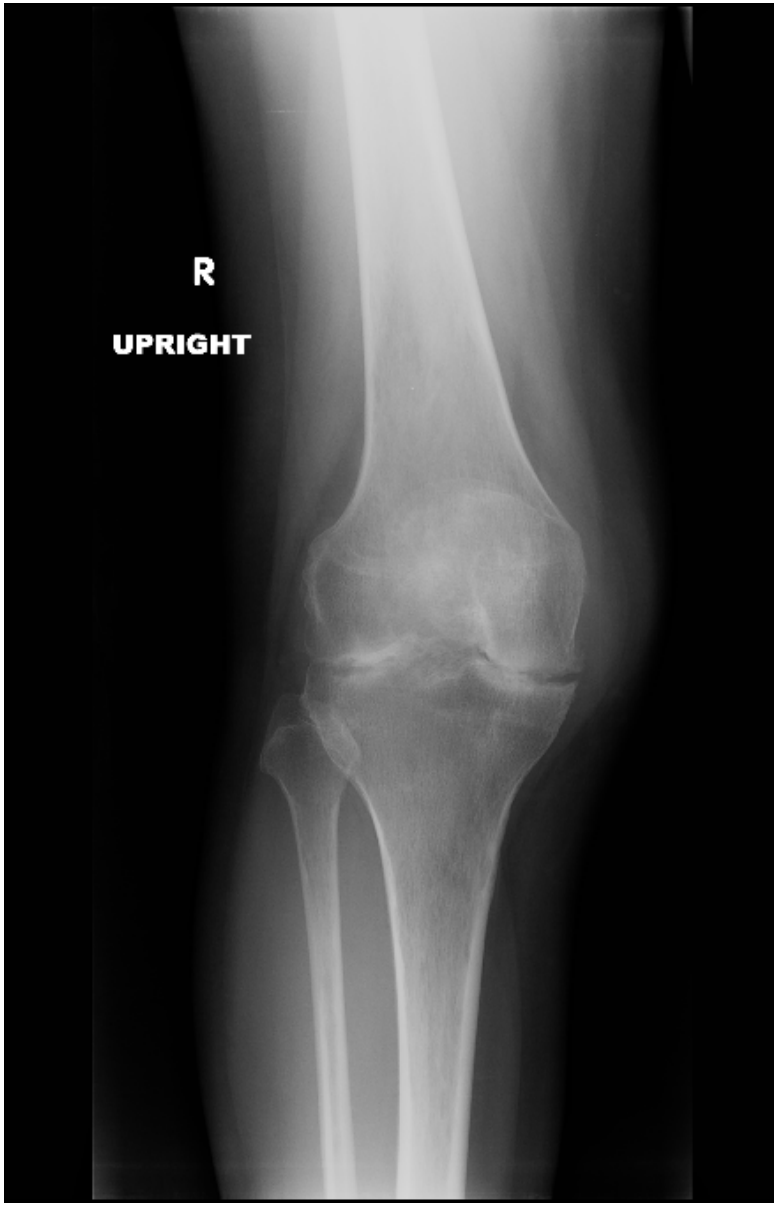


Early rheumatoid arthritis involving 2nd MCP joint. PA radiograph demonstrates diffuse 2nd MDP joint space narrowing with erosions of the radial aspect of the metacarpal head and 2nd proximal phalange.

Early erosive rheumatoid arthritic disease of feet. PA radiographs demonstrate erosions of 5th metatarsal heads bilaterally and symmetrically. There is diffuse inflammatory joint space narrowing of the 1st and 5th MTP joints.

Arthritis mutilans. Same patient as figure 1. PA radiographs of feet demonstrate advanced erosive disease of the MTP joints with “licked candystick” appearnce of distal metatarsals resulting in arthritis mutilans deformities.

Basilar invagination and atlantoaxial subluxation. Sagittal T1 (left) and sagittal CT (right) demonstrate basilar invagination the dens located cephalad and posterior to the tip of the clivus. The dens indents the brainstem. There is widening of the distance between the anterior arch of C-1 and the dens.



35 yo woman with rheumatoid arthrits: PA and lateral radiographs of the knees demonstrate diffuse tricompartmental joint space narrowing with suprapatellar effusion

What is the Natural History of RA and Its Treatment from the 30's to the Present Time?

Table 1.—Results of Follow-Up of 293 Patients With Rheumatoid Arthritis

	Year of follow-up* (% of patients)		
Course of disease	**1937**	**1947**	**1954**
In remission	17.2	16.9	13.2
Slight to moderate improvement	36.9	37.8	21.8
No change	26.8	11.6	2.3
Progression	19.2	33.8	62.6
Total no. of patients	239	225	174

*Patients were entered into this prospective study between 1930 and 1936.
Modified from Short and associates. [5] By permission of Harvard University Press.

Table 2.—500 Patients With Rheumatoid Arthritis: Progression of Disease Over Years of Follow-up

Patients, no.	500	403	387	246	176
Point in time after first visit	1st Visit	1-5 Years	6-10 Years	11-15 Years	16+ Years
Stages 1 and 2, %	82	74	58	50	45
Stages 3 and 4, %	18	26	42	50	55
Employment, Patients, no.	451	359	820	205	148
Full Time, %	53	61	57	56	50
Part time, %	19	15	16	15	18
None, %	28	24	27	29	32

From: Ragan C, Farrington E: The clinical features of rheumatoid arthritis. JAMA 181:663-667, 1962, p. 664.

Long-Term Outcome of Treating Rheumatoid Arthritis: Results After 20 Years

D. L . Scott

B. L. Coulton[1]

D. P. M. Symmons[1]

A. J. Popert[1]

Department of Rheumatology, St Bartholomew's Hospital, West Smithfield, London EC1A7BE; and Droitwich Centre for Rheumatic Diseases, Highfield Hospital, Droitwich

Table 3.—Changes in Functional Class During 20 Years of Study

Functional Class	Initial	5 Years	10 Years	20 Years
I/II	26	60	60	19
III	70	41	19	29
IV/V	16	10	11	20
Dead	0	1	17	37
Lost to follow-up	0	0	5	7

From: Scott DL, Coulton BL, Symmons DPM, et al: Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1:1108-1111, 1987, p. 1109.

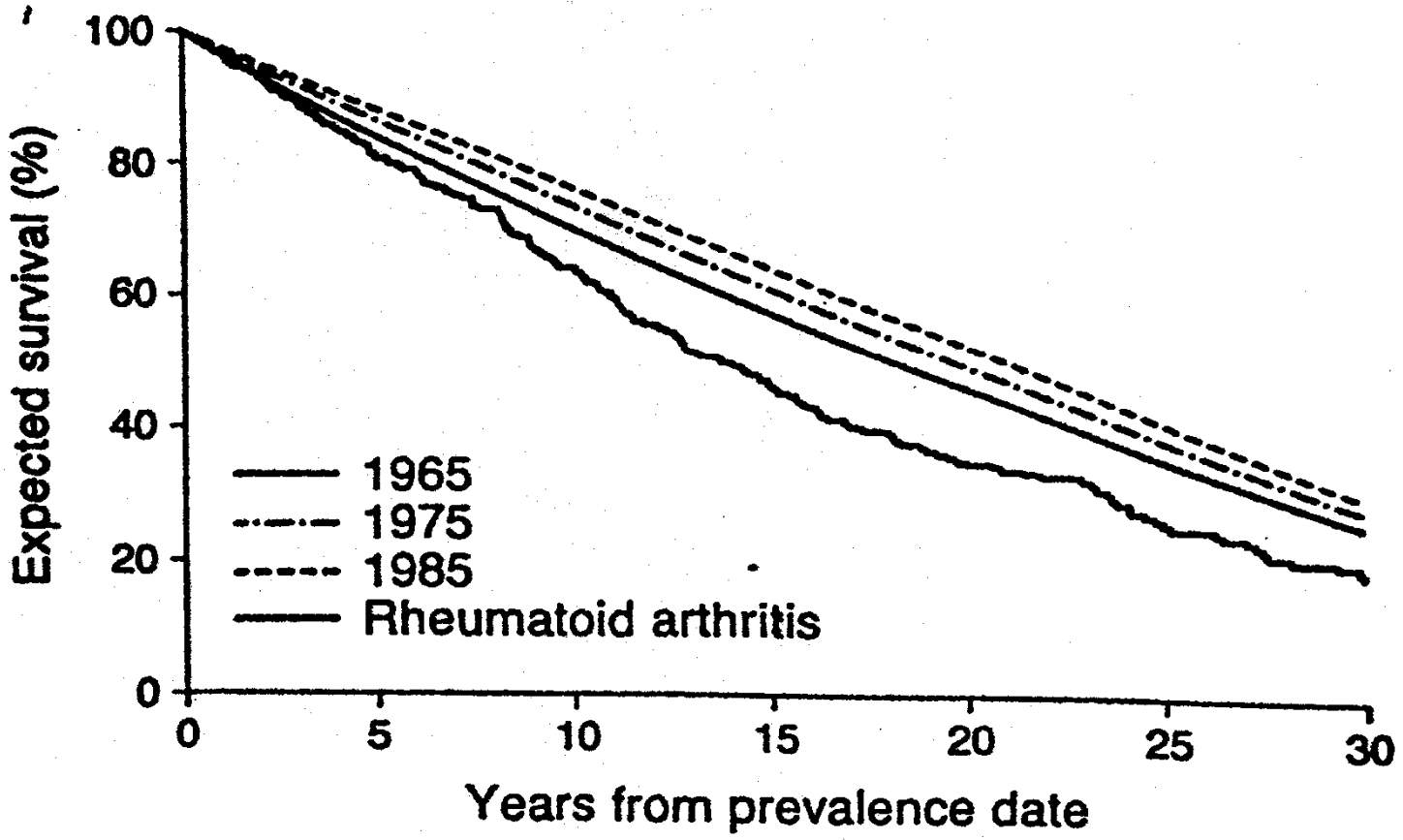
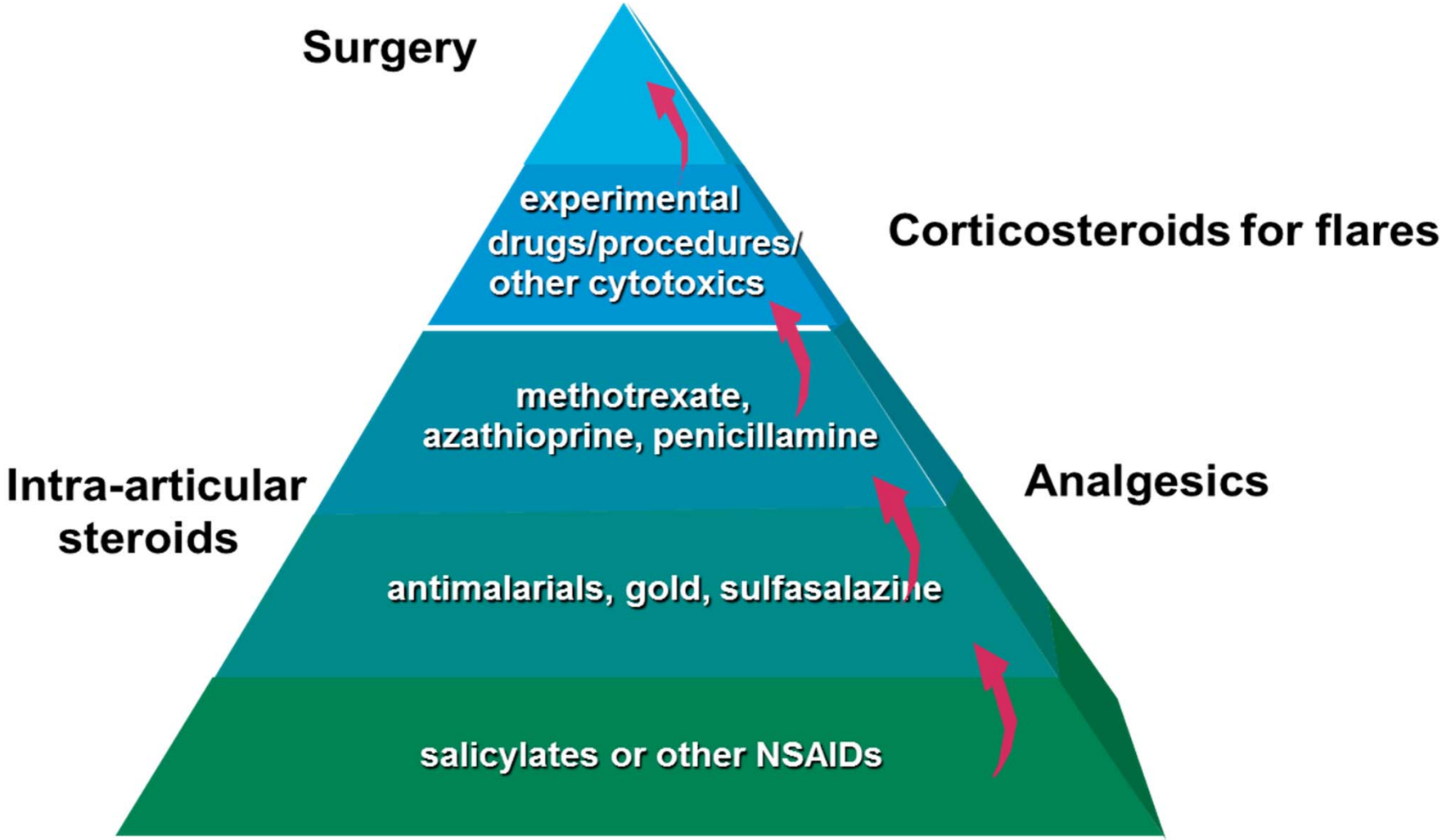


Figure 5. Survival for the general population of Rochester, MN, residents (age and sex similar to that of the RA prevalence cohorts) beginning January 1, 1965, January 1, 1975, and January 1, 1985, compared to survival of the 1965, 1975, and 1985 RA prevalence cohorts combined.

The Traditional Treatment Pyramid for RA: Sequential Drug Therapy



Healey LA, Wilske KR. *Rheum Dis Clin North Am.* 1989;15:615-619.

In the 1990's RA Clinical Outcome Changed – How and why did this happen?

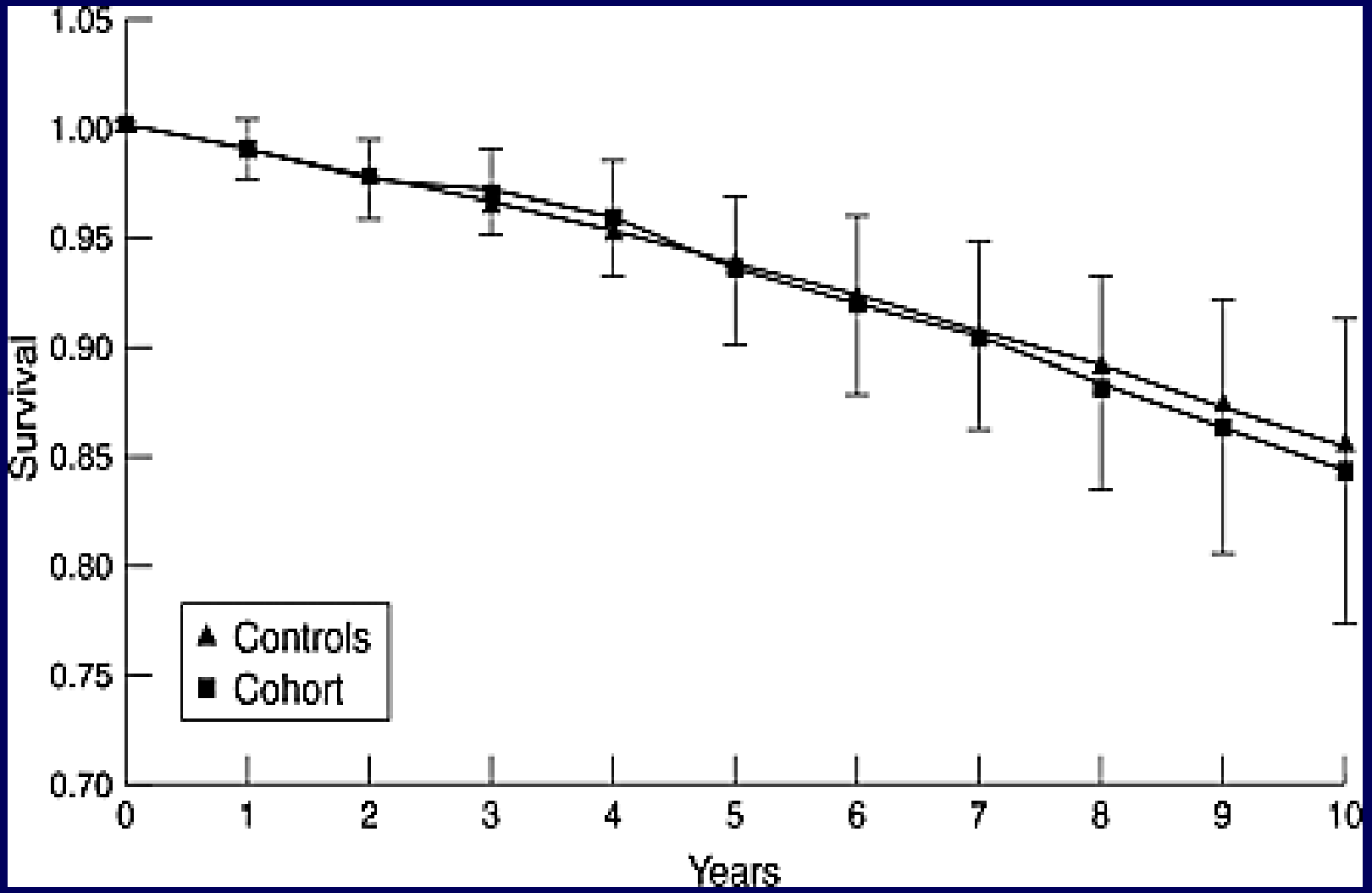


Figure 2 Kaplan-Meier survival curves of patients with recent onset rheumatoid arthritis compared with the general population of the Netherlands, matched for age and sex. Confidence intervals (95%) of the study group are shown.

Arthritis & Rheumatism Vol.48, 1 Pages: 54-58

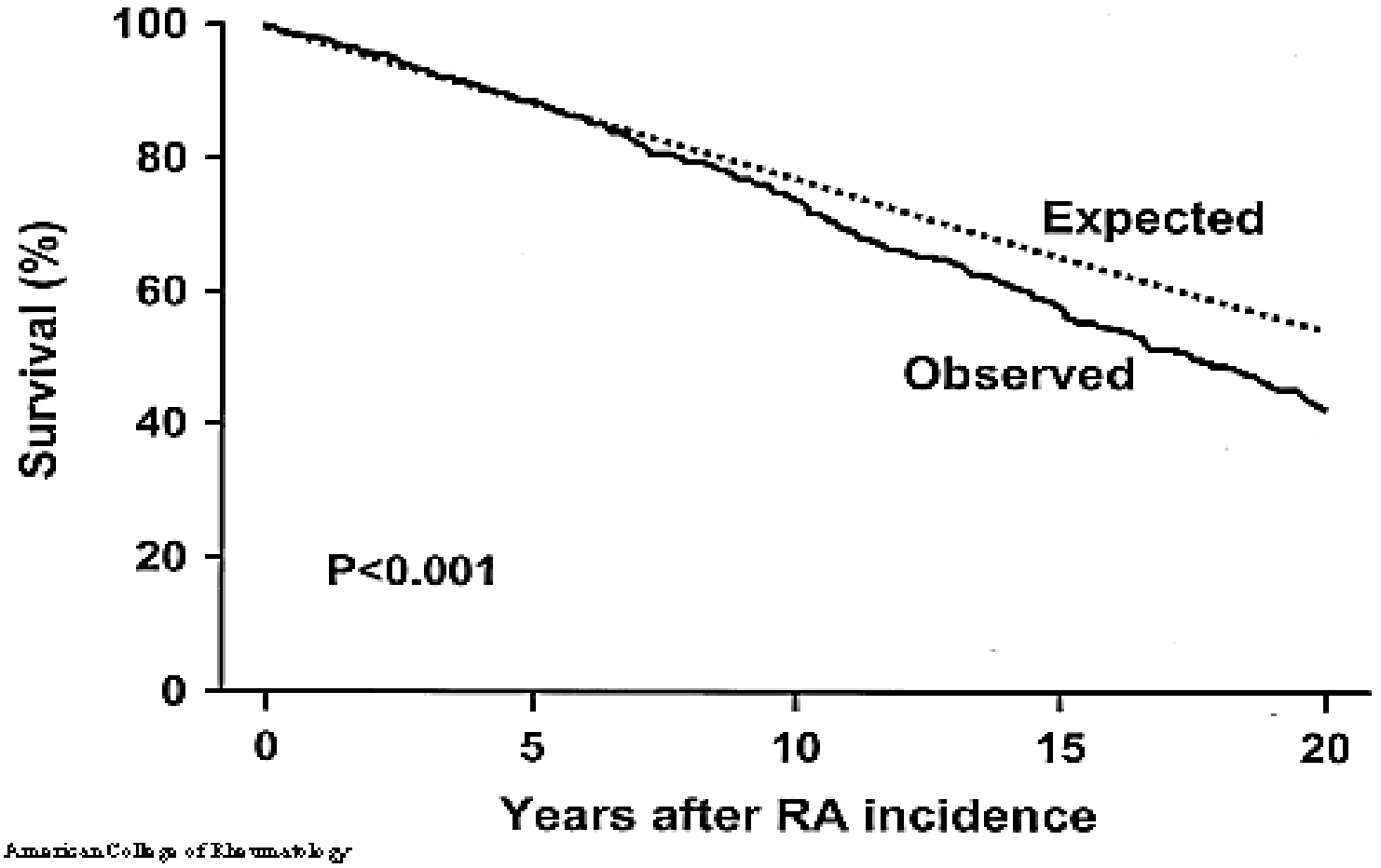


Figure 1. Survival among Rochester, Minnesota residents first diagnosed with rheumatoid arthritis (RA) between January 1, 1955 and December 31, 1994 (n = 609), compared with expected survival.

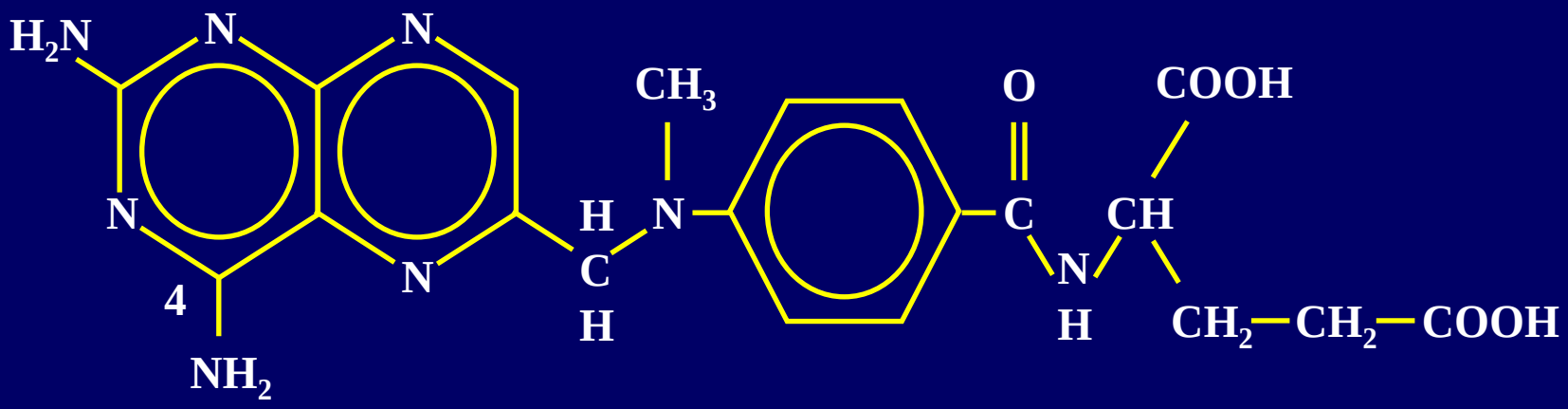
There Are 5 Reasons For This Change: in order of Importance

What were we taught by a small study in the UK?

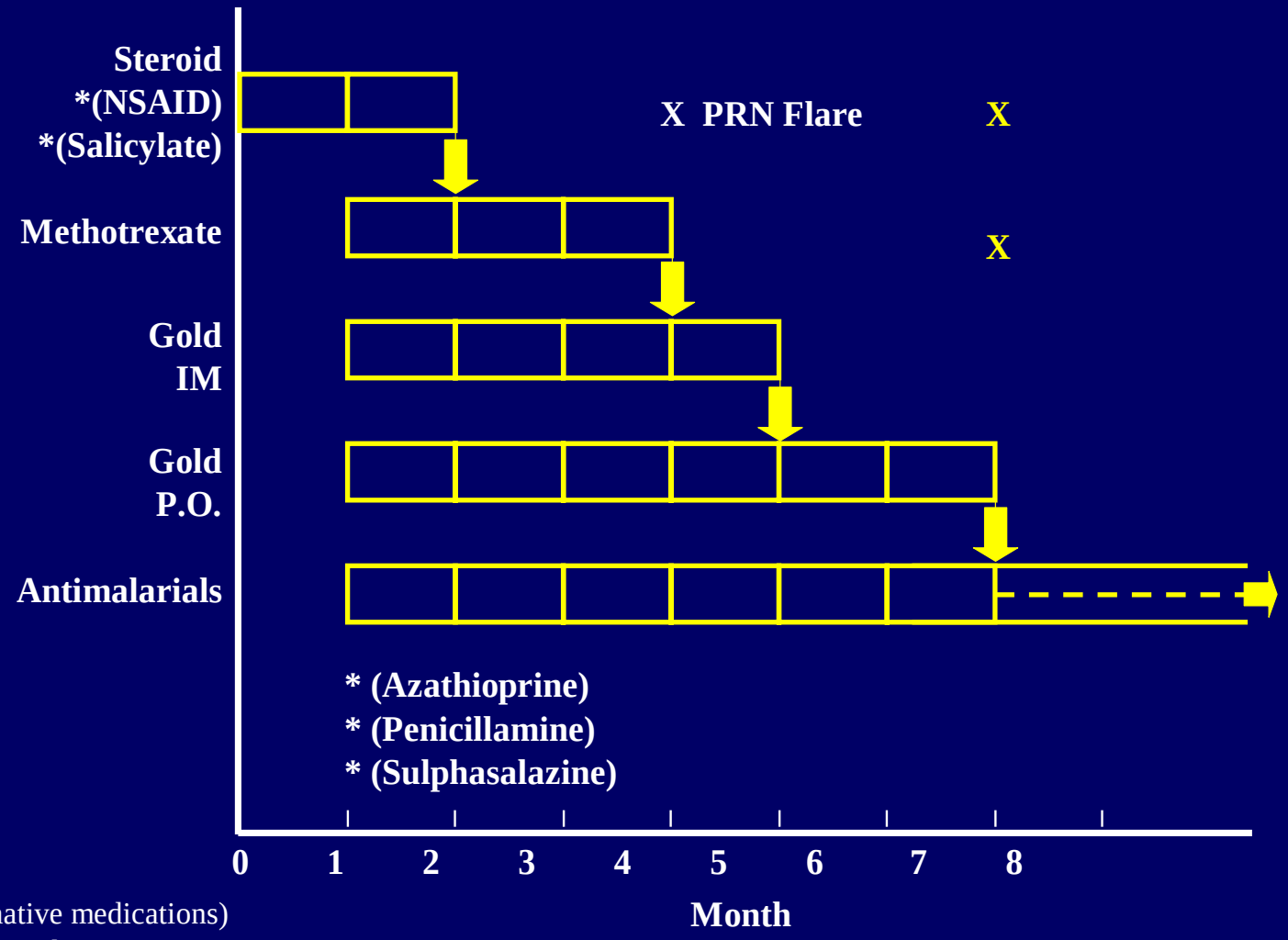
- Monozygotic twins, discordant for RA, were evaluated by comparing their smoking history between twins with RA and their unaffected co-twin.
- Smokers with RA: 12/13
- Non-smokers with RA: 1/13
- Although most twin pairs were concordant for smoking history, there was a strong association between ever smoking and RA in the MZ pairs

Silman et al A&R 39;732-735, 1996

Methotrexate

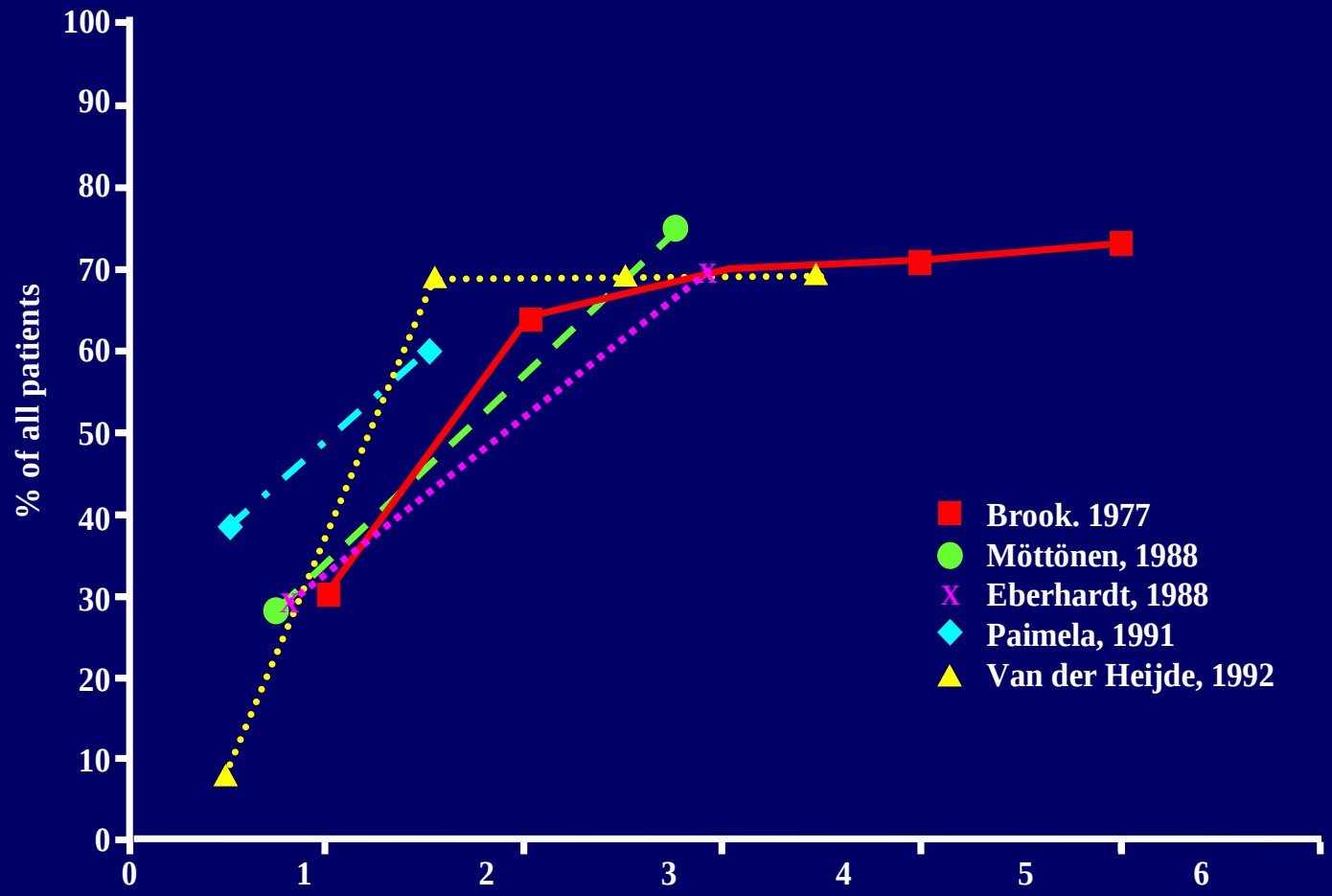


Arthritis Medications



*(Alternative medications)
Wilske, Healey, 1989.

Proportion of Patients With RA With Joint Erosions After Average Disease Durations of 6 Months to 5 Years. Note the Proportion With Erosions Changes Little After 2 Years of RA



Van der Heijde, 1995.
(Adapted With Permission)

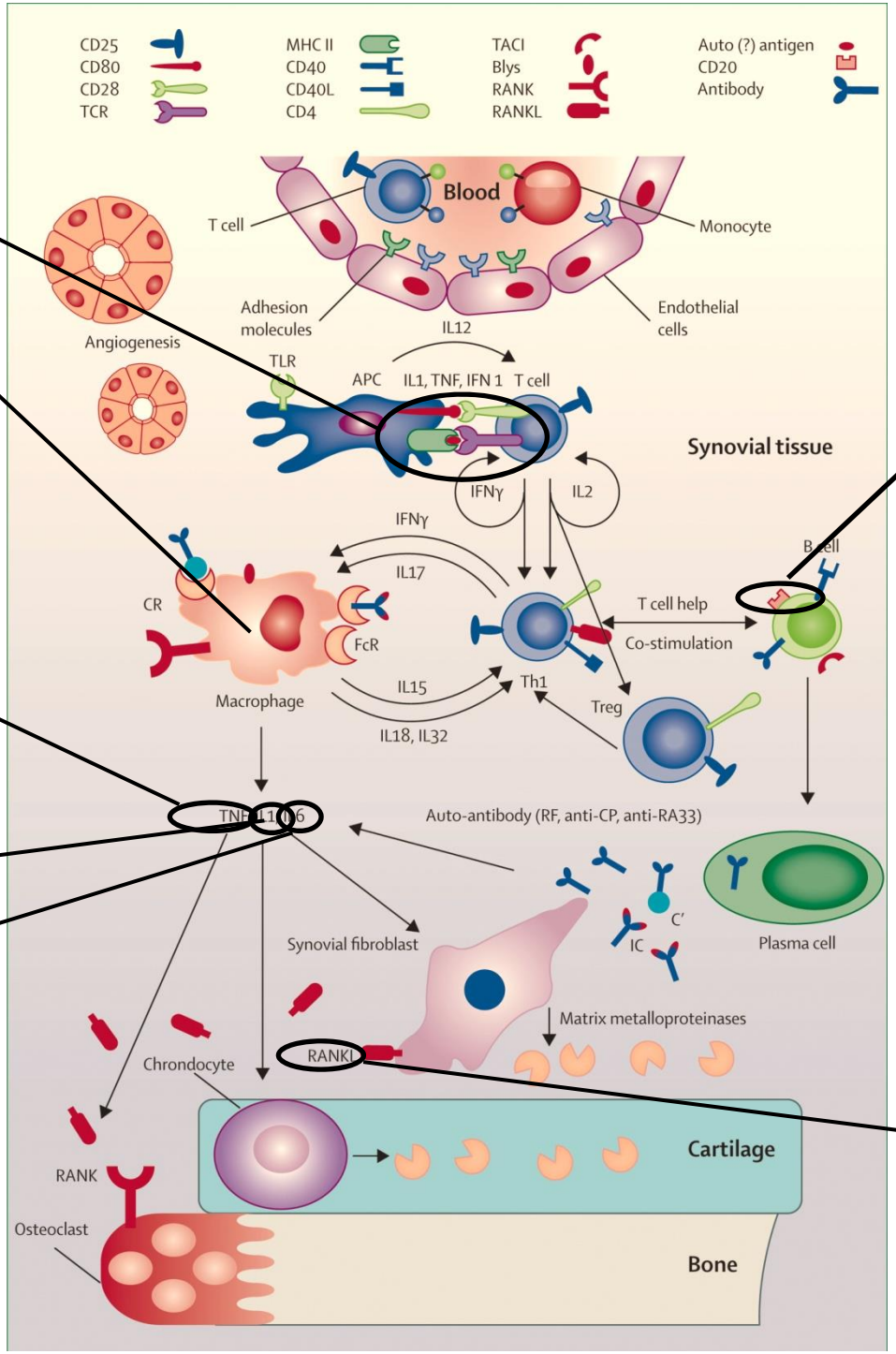
Abatacept
CTL4A IgG

JAK Inhibition
Zeljanz

TNF-blocking agents; monoclonal Ab, receptor fusion protein

Anakinra
anti-IL1 receptor

Tocilizumab
anti-IL6 receptor



Rituximab
monoclonal Ab
against CD20 on
B-cells

Denosumab
anti RANKL
monoclonal Ab

What Did Rheumatologists Do To Make These Changes?

- Did not wait until patients fulfilled classification criteria
- Treat early
- Treat aggressively
- Use combinations of drugs (like oncologists)
- Focus on putting patients into remission (or at least a low disease activity state)
- We took the lead from Europe but proof came later

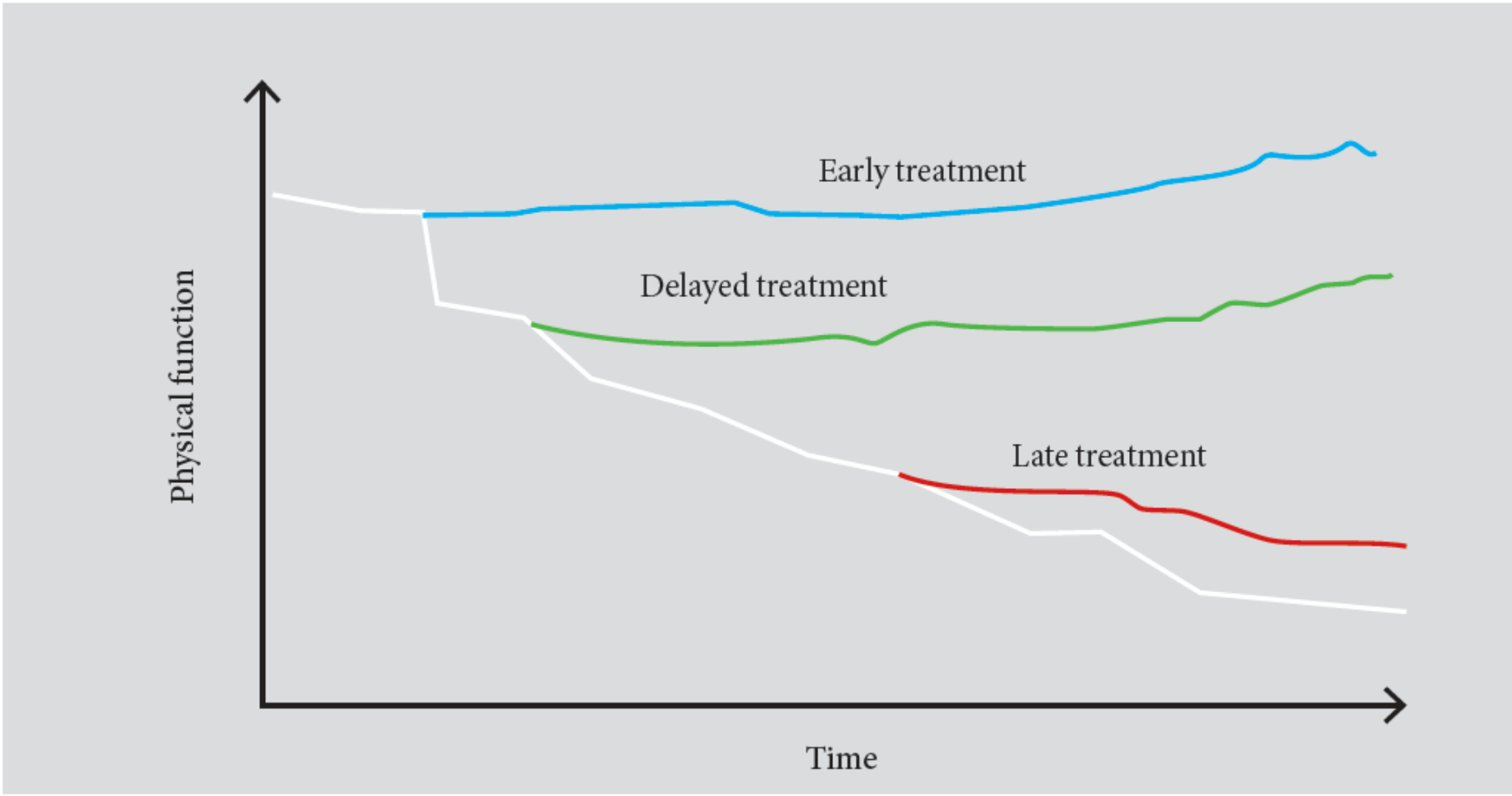


Figure 1.1 Why is early classification of rheumatoid arthritis needed? Over time, structural damage increases and physical function declines if rheumatoid arthritis (RA) is not treated effectively. While institution of therapy in late RA can improve function to only a very small extent, earlier treatment has the potential to stabilize physical function before permanent disability occurs.

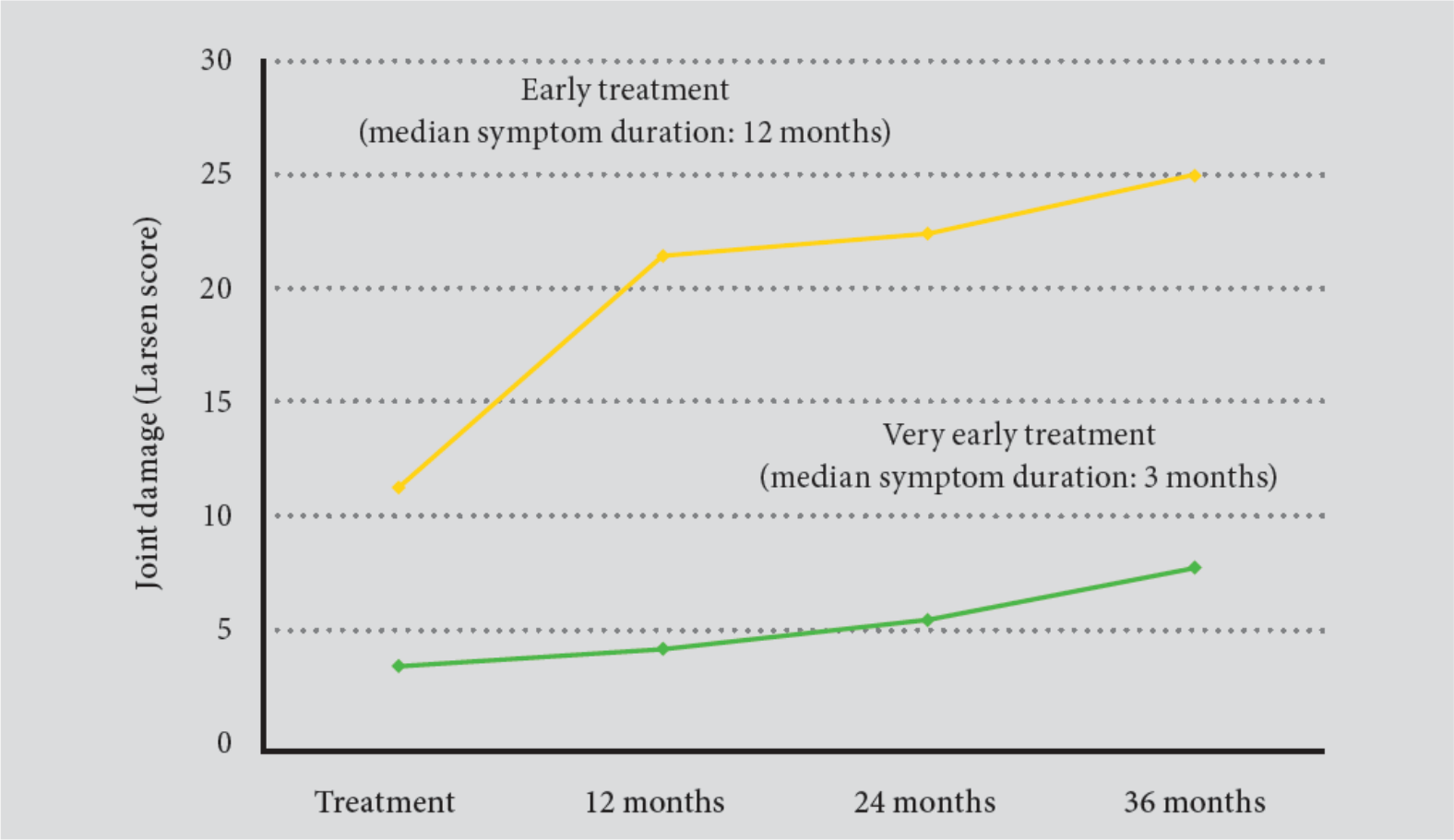


Figure 1.2 The importance of starting rheumatoid arthritis therapy very early. Even short delays in treatment initiation in patients with rheumatoid arthritis (RA) can lead to a considerable increase in structural damage over the course of 3 years. The yellow line shows that progression in Larson radiographic scores is already substantial in patients receiving early treatment initiation (ie, with a median symptom duration of only 12 months). In very early treatment initiation (ie, with a median symptom duration of 3 months, as represented by the course of the green line), the slope of progression is flattened and after 3 years, these patients did not reach the degree of structural damage that the early treatment initiation group already had at baseline despite only a 9-month delay in treatment. Adapted with permission from Nell et al [2] ©Oxford University Press.

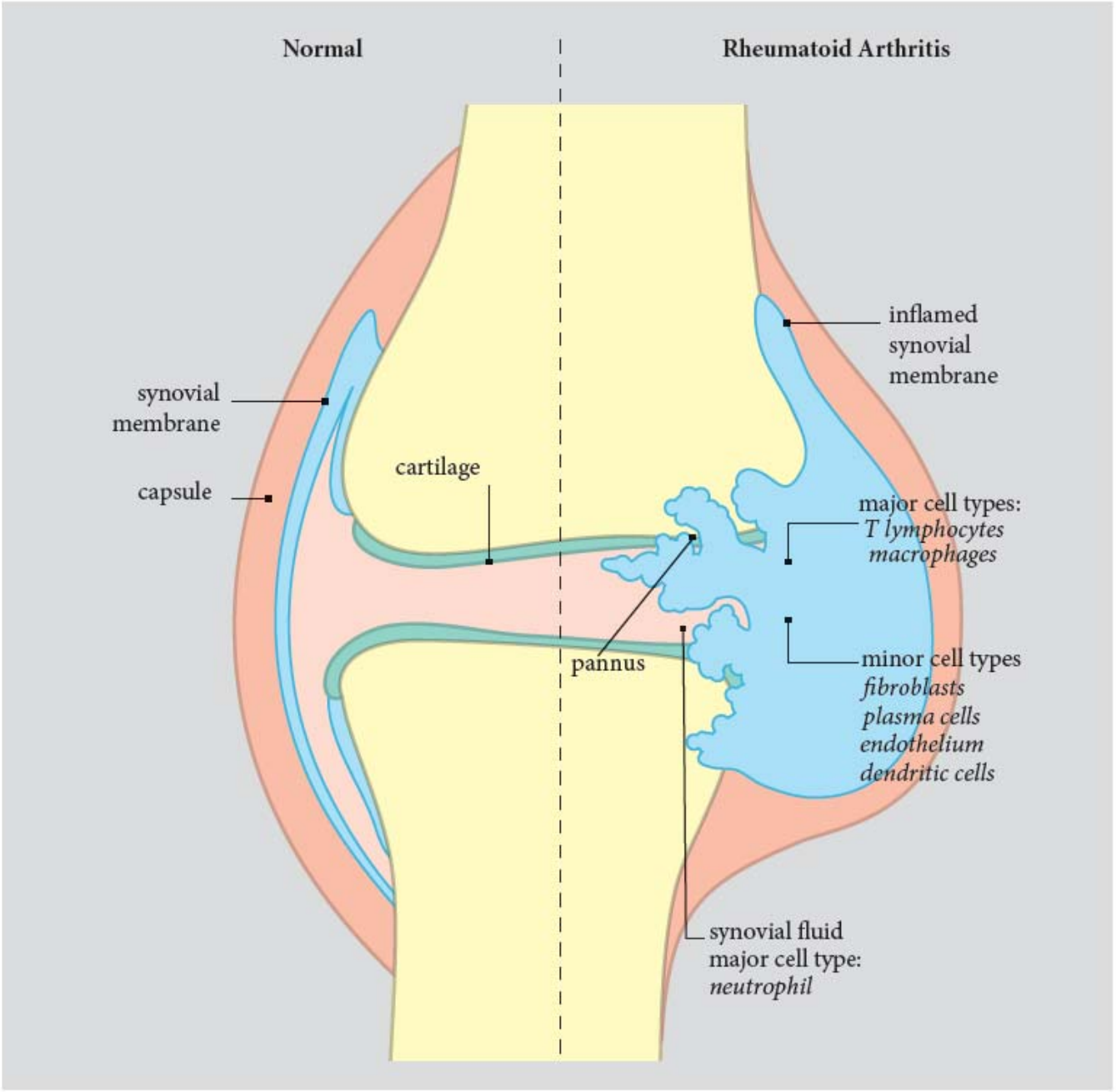


Figure 3.1 Synovial joint in health and rheumatoid arthritis indicating cellular components and sites of destruction in diseased joint. Reproduced with permission from Taylor [16] ©Humana Press.

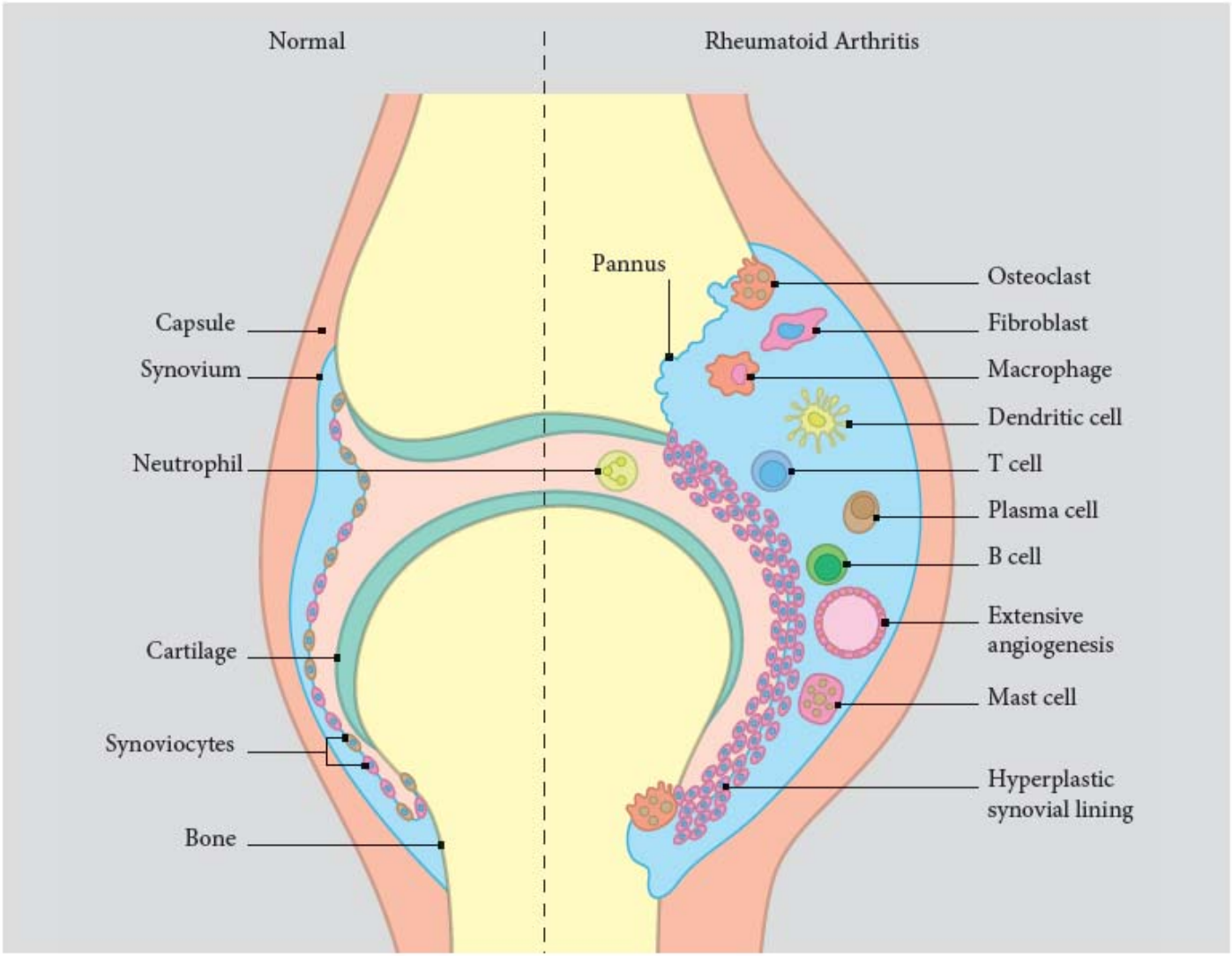


Figure 12.1 Schematic representation of a normal joint and joint with rheumatoid arthritis. The picture shows the thin lining layer and synovial membrane in a normal joint compared with the widened synovial membrane with hyperplasia of the lining layer in rheumatoid arthritis (RA; right half). Many cell populations enter the synovium through activated vasculature (endothelial cells) and contribute to the inflammatory process. B-cells, T-cells, monocytes/macrophages, and dendritic cells are all part of the process, as are mast cells and synovial fibroblasts. The hyperplastic synovial membrane can invade bone subchondrally and also lead to cartilage destruction. Reproduced with permission from Smolen and Steiner [1] ©Nature.

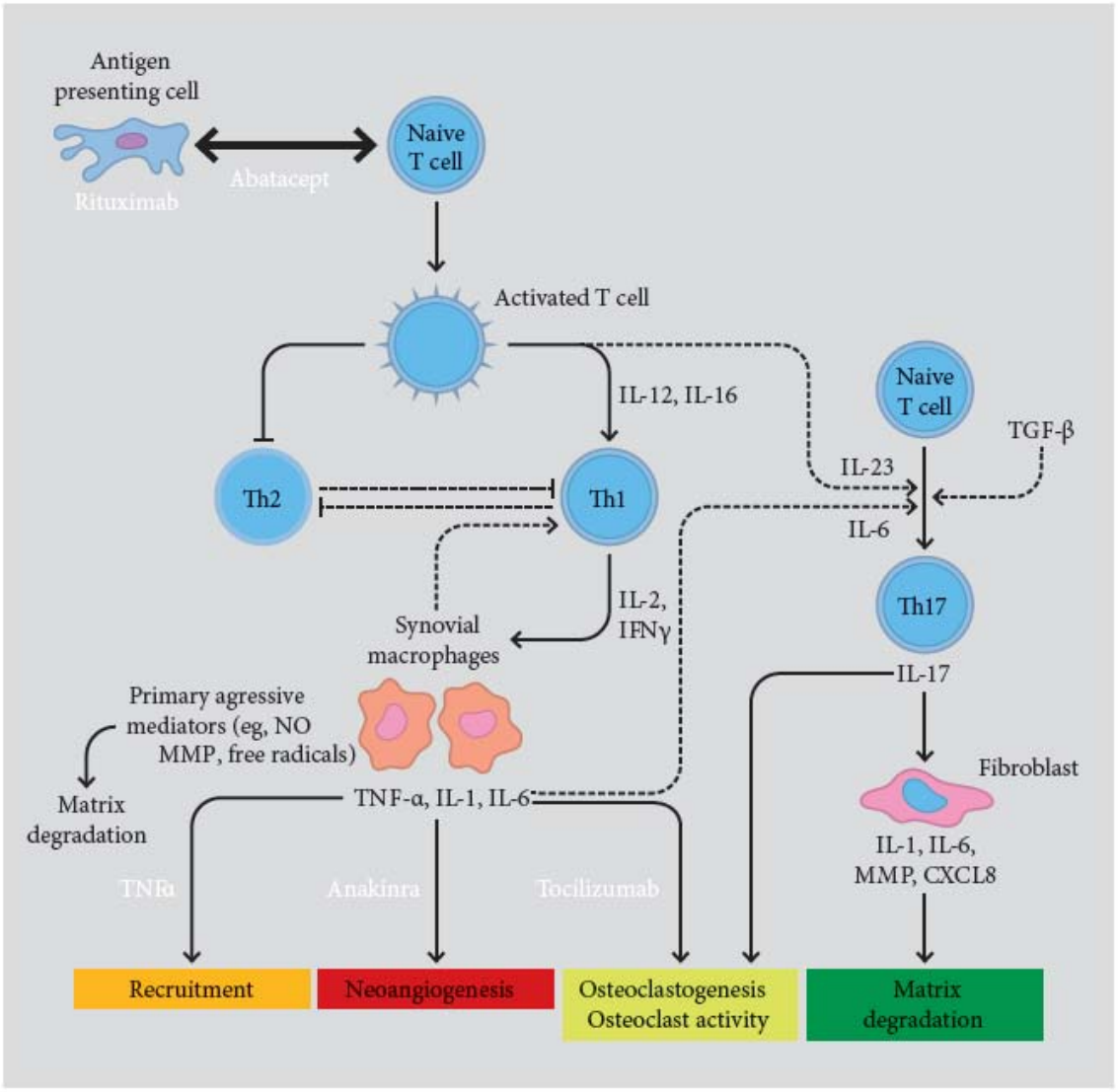


Figure 10.1 Targets of action of biological disease-modifying anti-rheumatic drugs. The first group of biologic therapies acts downstream on inflammatory cytokines (tocilizumab, TNF-α blockers, anakinra). The second group acts on lymphocyte biology, either by preventing the T-cell activation in interrupting the CD28–CD80/CD86 co-stimulatory pathway (abatacept) or by deleting CD20+ B lymphocytes which compromises antigen presentation and T- and B-cell activation and immunoglobulin secretion (rituximab). CXCL, chemokine ligand; IL, interleukin; IFNγ, interferon gamma; TGF-β, transforming growth factor beta; Th, T helper cell; TNF-α, tumor necrosis factor alpha; MMP, matrix metalloproteinases; NO, nitric oxide. Reproduced with permission from Confavreux and Charpurlat [34] ©Springer.

Over-riding principle in RA management

Is it timing, or is it the drugs?

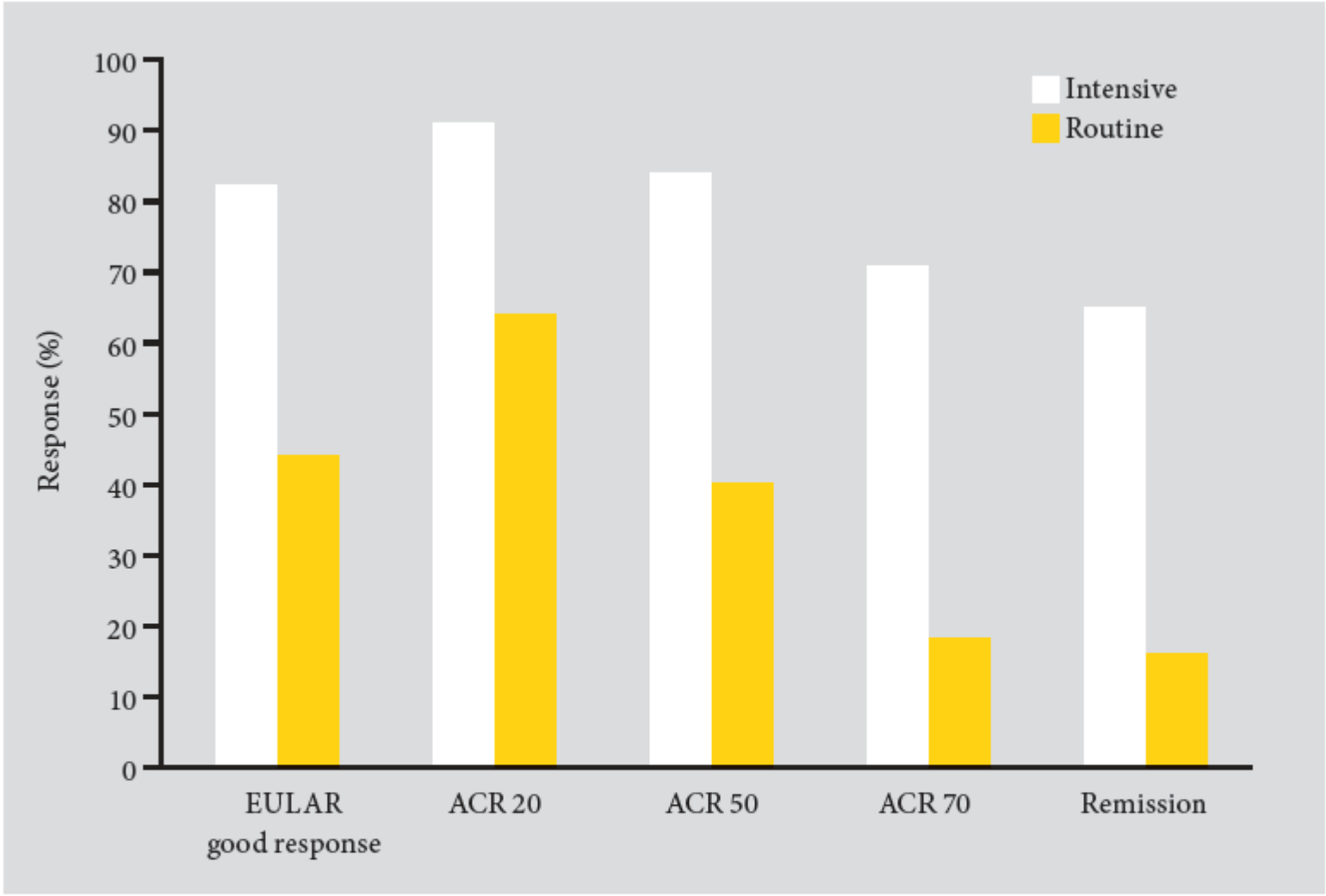


Figure 3.13 Intensive versus routine monitoring: results from the TIght COntrol in Rheumatoid Arthritis (TICORA) study. In the TICORA study, patients in the intensive treatment group experienced significantly greater EULAR and ACR responses and higher remission rates than the control group after 18 months of follow-up. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism. **Reproduced with permission from Grigor et al [42] ©Lancet.**

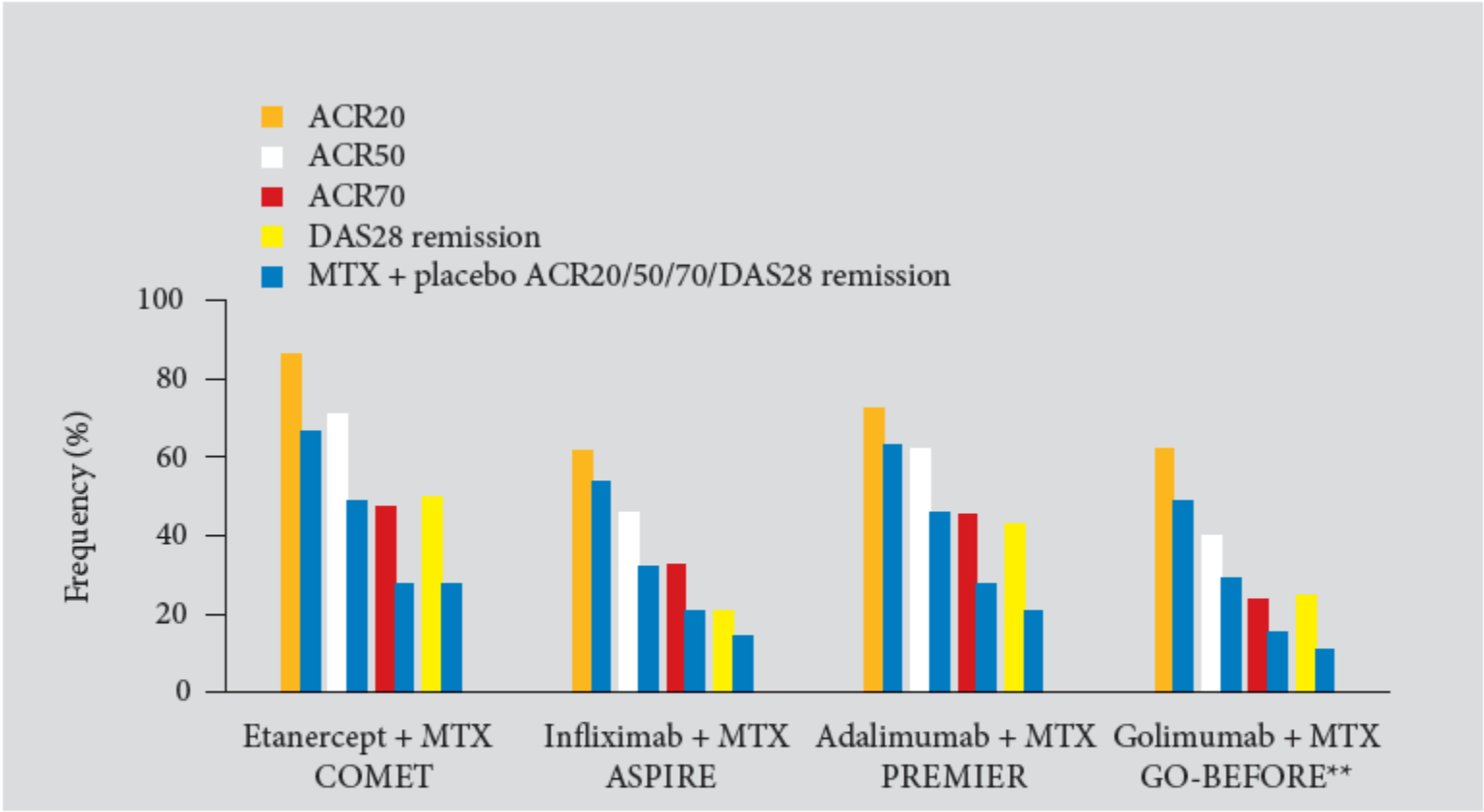


Figure 10.12 Efficacy of tumor necrosis factor inhibitors in combination with methotrexate at 1 year in methotrexate-naïve patients with early rheumatoid arthritis and poor prognostic factors. Results are shown for licensed dose groups. **Study duration in GO-BEFORE was 24 weeks (outcomes presented for study end). ACR 20/50/70, American College of Rheumatology 20%; 50%, and 70% improvement criteria; DAS28, disease activity score for 28 joints; MTX, methotrexate.

If we use biological drugs, what are the risks?

Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies

Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials

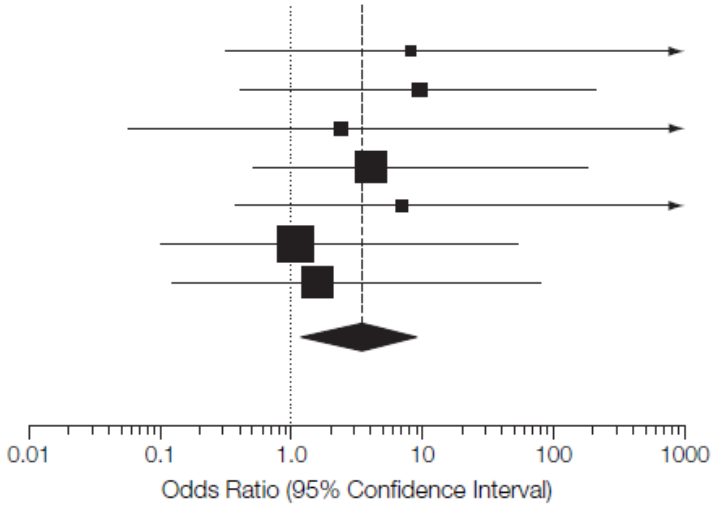
Tim Bongartz, MD
Alex J. Sutton, PhD
Michael J. Sweeting, MSc
Iain Buchan, MD, MFPH
Eric L. Matteson, MD, MPH
Victor Montori, MD, MSc

JAMA. 2006;295:2275

Figure 2. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis

Source	Malignancies, No./Total: Anti-TNF	Malignancies, No./Total: Placebo	Odds Ratio (95% Confidence Interval)
Lipsky et al,[9] 2000	5/342	0/86	7.57 (0.30-Infinity)
Furst et al,[8] 2003	4/318	0/318	9.11 (0.40-199.49)
Weinblatt et al,[11] 2003	1/209	0/62	2.29 (0.06-Infinity)
Keystone et al,[6] 2004	8/419	1/200	3.87 (0.51-172.73)
St Clair et al,[7] 2004	4/749	0/291	6.58 (0.36-Infinity)
Van de Putte et al,[33] 2004	4/434	1/110	1.01 (0.10-50.39)
Westhovens et al,[34] 2004	3/721	1/361	1.50 (0.12-79.18)
Total	**29/3192**	**3/1428**	**3.29 (1.19-9.08)**

Test for overall effect:
Mantel-Haenszel $\chi^2 = 5.2$; $P = .02$

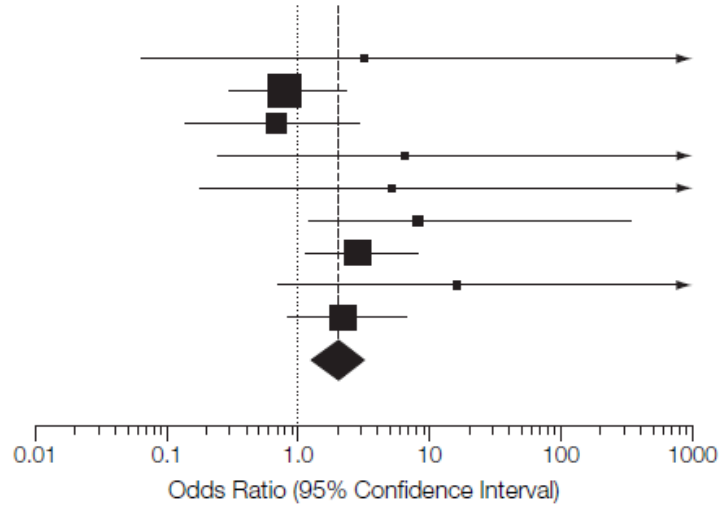


TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

Figure 3. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Serious Infections in Patients With Rheumatoid Arthritis

Source	Serious Infections, No./Total		Odds Ratio (95% Confidence Interval)
	Anti-TNF	Placebo	
Maini et al,[32] 1998	2/87	0/14	3.13 (0.06-Infinity)
Lipsky et al,[9] 2000	21/342	7/86	0.76 (0.30-2.18)
Furst et al,[8] 2003	4/318	6/318	0.66 (0.14-2.83)
Van de Putte et al,[10] 2003	4/214	0/70	6.33 (0.30-Infinity)
Weinblatt et al,[11] 2003	3/209	0/62	4.93 (0.19-Infinity)
Keystone et al,[6] 2004	16/419	1/200	7.90 (1.21-332.96)
St Clair et al,[7] 2004	40/749	6/291	2.68 (1.11-7.81)
Van de Putte et al,[33] 2004	11/434	0/110	15.34 (0.71-Infinity)
Westhovens et al,[34] 2004	25/721	6/361	2.13 (0.84-6.39)
Total	**126/3493**	**26/1512**	**2.01 (1.31-3.09)**

Test for overall effect:
Mantel-Haenszel $\chi^2 = 9.1$; $P = .002$



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

Table 4. Effect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patients With Rheumatoid Arthritis, Stratified by Dose Group

Adverse Event	Odds Ratio (95% Confidence Interval)*			
	All Doses of Anti-TNF Antibody Therapy vs Placebo	Low-Dose Anti-TNF Antibody Therapy vs Placebo†	High-Dose Anti-TNF Antibody Therapy vs Placebo‡	High-Dose‡ vs Low-Dose† Anti-TNF Antibody Therapy
≥1 Malignancy	3.3 (1.2-9.1)	1.4 (0.3-5.7)	4.3 (1.6-11.8)	3.4 (1.4-8.2)
≥1 Serious infection	2.0 (1.3-3.1)	1.8 (1.1-3.1)	2.3 (1.5-3.6)	1.4 (1.0-2.0)

Abbreviation: TNF, tumor necrosis factor.
*Pooled odds ratio based on a fixed-effects Mantel-Haenszel model for the all-doses estimate and based on high-dose/low-dose stratification.
†Infliximab, ≤3 mg/kg every 4 weeks, or adalimumab, 20 mg/wk.
‡Infliximab, ≥6 mg/kg every 8 weeks, or adalimumab, 40 mg every other week.

Lancet 2015; 385:258-65

Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

Jasvinder A Singh, Chris Cameron*, Shahrzad Noorbaloochi, Tyler Cullis, Matthew Tucker, Robin Christensen, Elizabeth Tanjong Ghogomu, Doug Coyle, Tammy Clifford, Peter Tugwell, George A Wells*

Controversy: conflicting data among meta-analyses. What about a super duper mega meta-analysis!

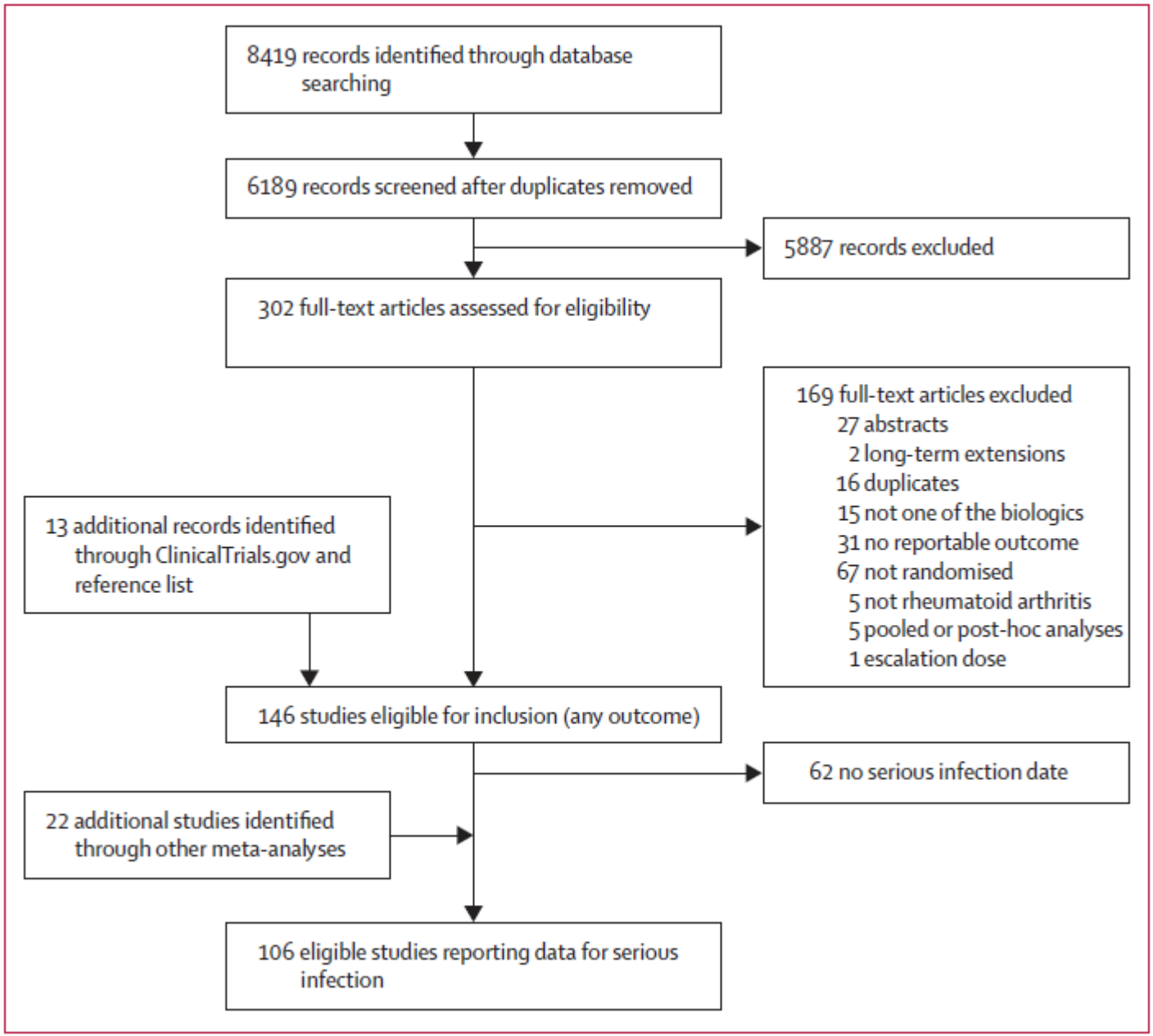


Figure 1: **Study selection**

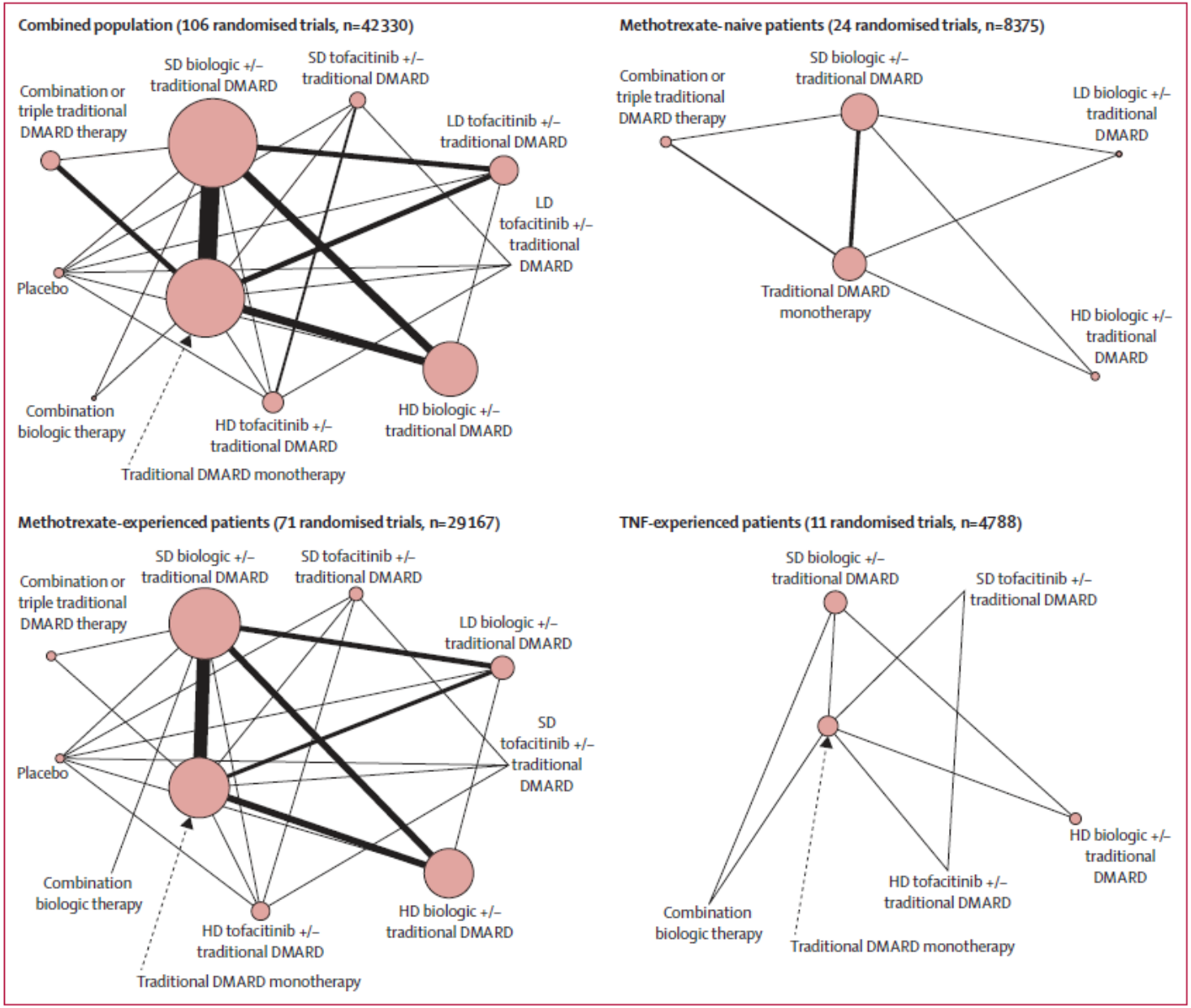


Figure 2: **Evidence networks for serious infection in populations**

The width of the lines is proportional to the number of randomised trials being compared in each pair of treatments. The size of each treatment node is proportional to the number of participants (sample size). Doses are defined in the appendix. DMARD=disease-modifying antirheumatic drugs. SD=standard dose. HD=high dose. LD=low dose.

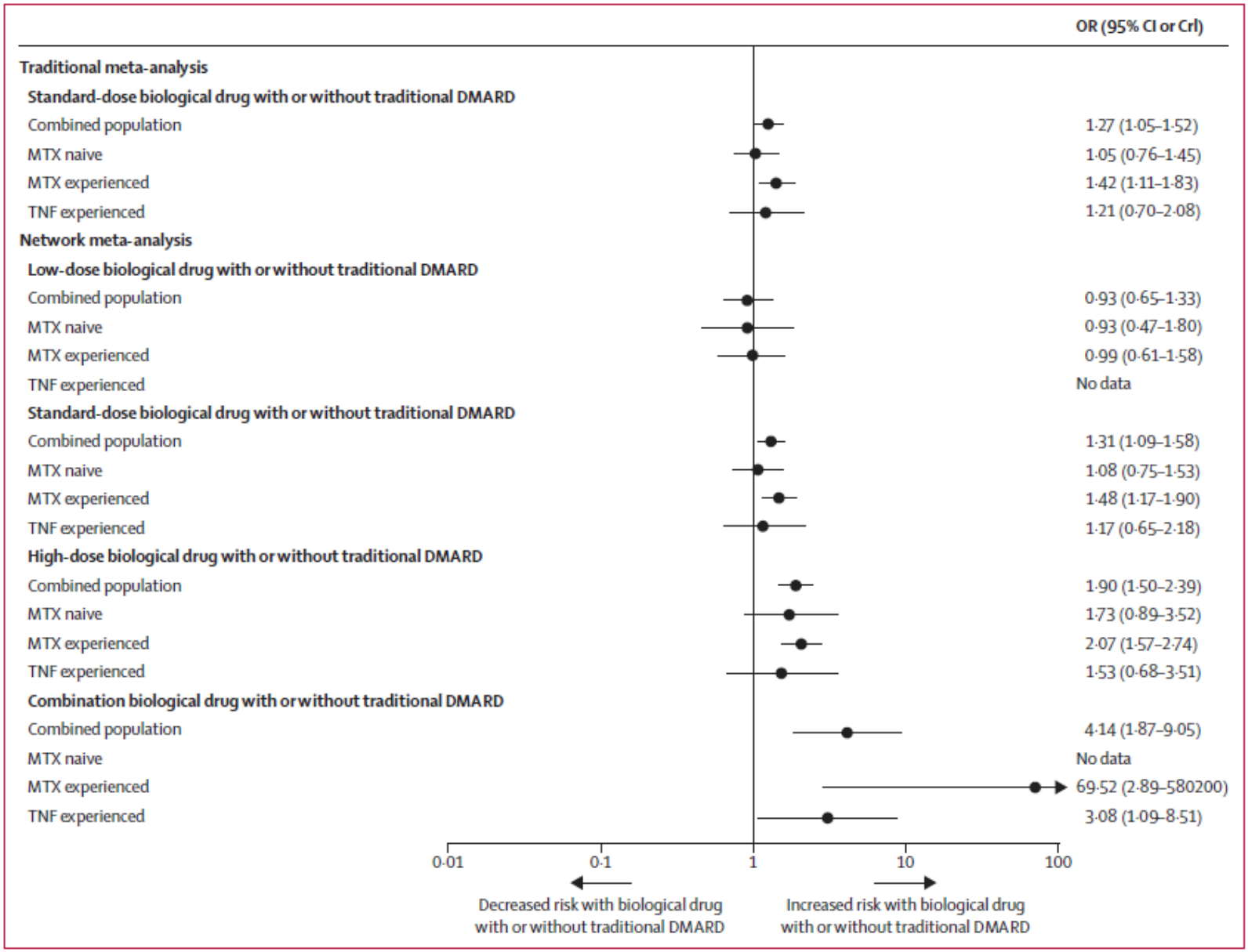


Figure 3: **Traditional meta-analysis and network meta-analysis**

Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. Data for the traditional meta-analysis are OR (95% CI) and data for the network meta-analysis are OR (95% CrI). OR=odds ratio. CrI=credible interval. DMARD=disease-modifying antirheumatic drugs.

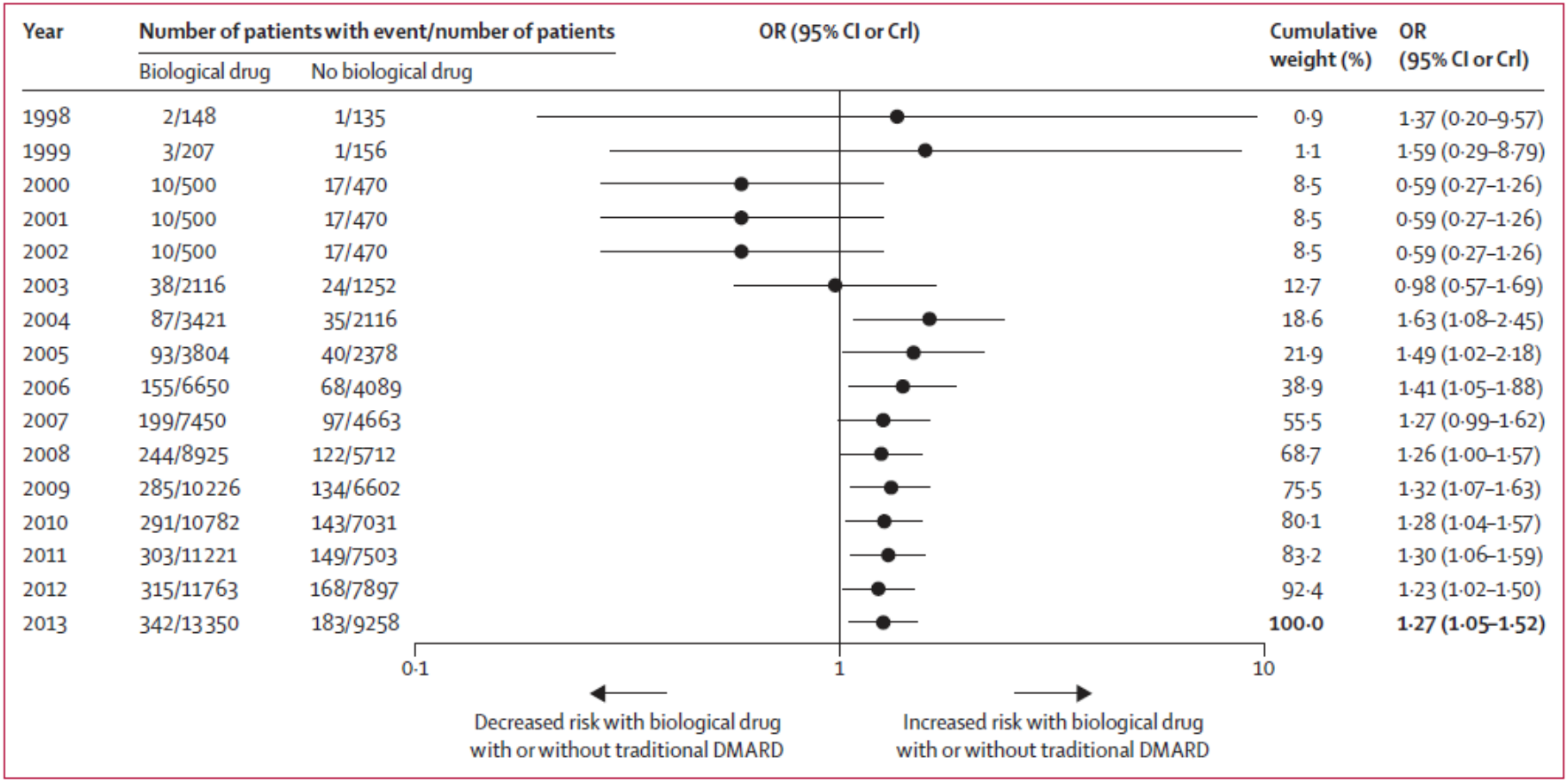


Figure 4: **Cumulative meta-analysis**

Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. OR=odds ratio. DMARDs=disease-modifying antirheumatic drugs.

Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?

Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A, Listing J

Ann Rheum Dis 2011;**70**:1914–1920. doi:10.1136/ard.2011.151043

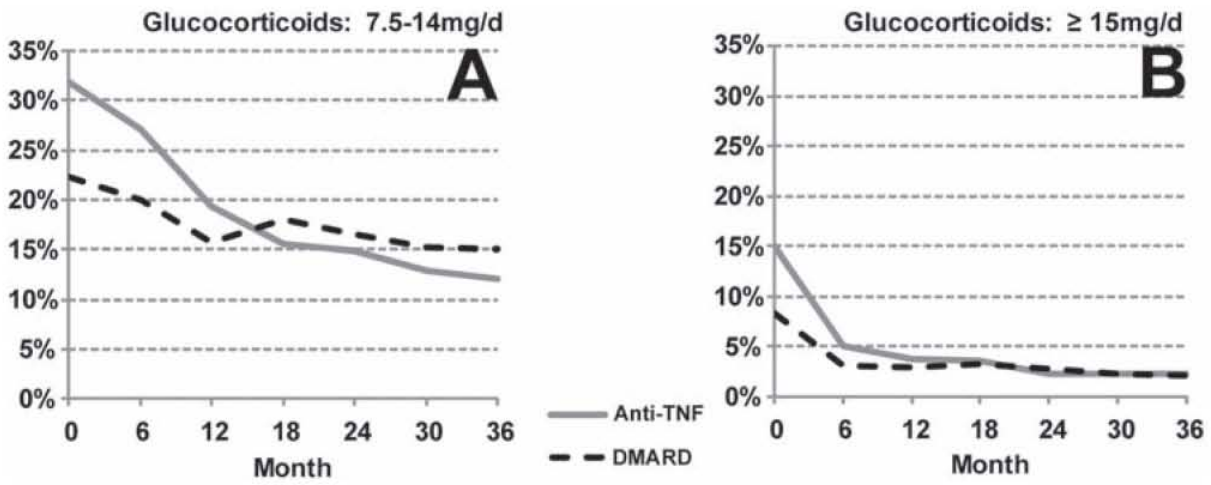


Figure 2 Decline in co-medication with glucocorticoids in patients who received a dose of (A) 7.5–14 mg/day or (&) ! 15 mg/day. DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

Time dependent decline in the use of steroids in an observational cohort of DMARD and TNF users

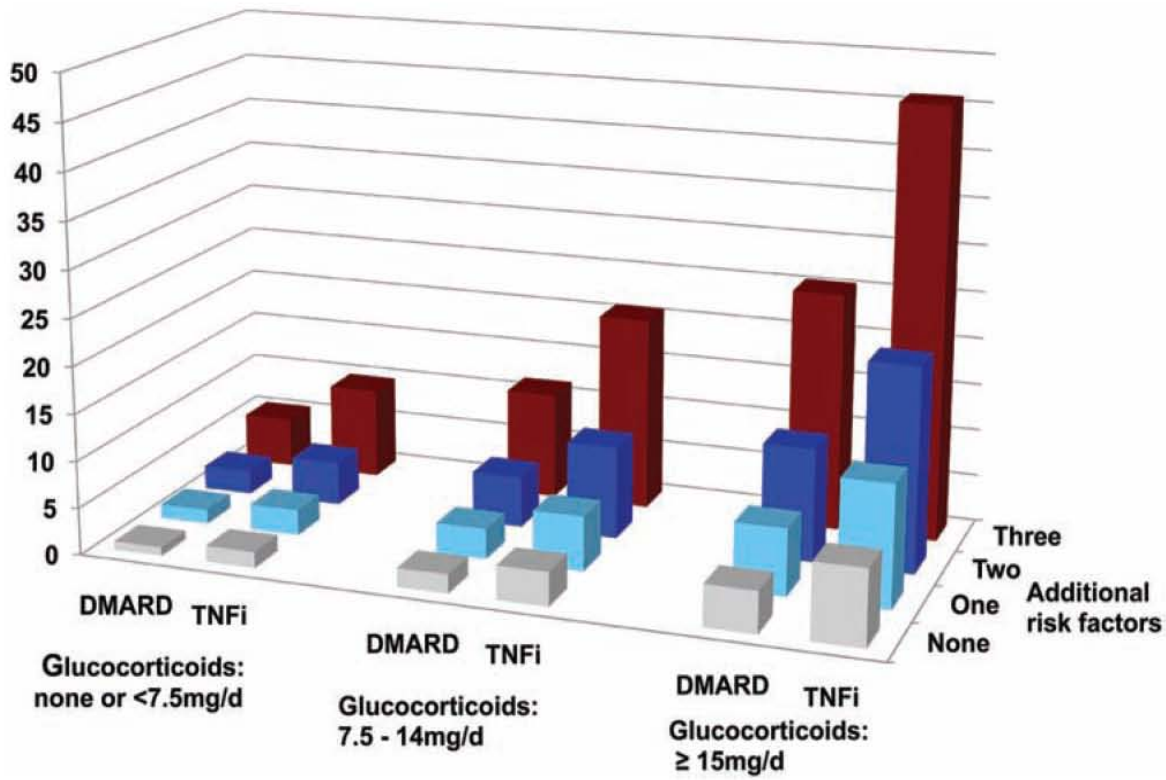
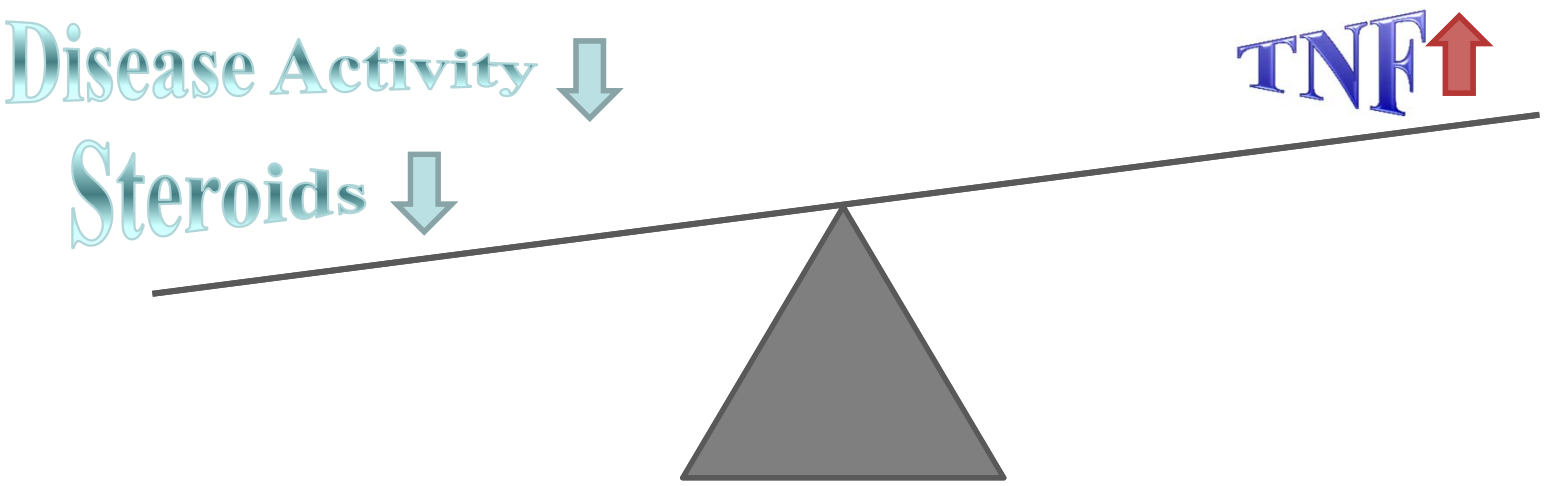


Figure 3 Estimated incidences of serious infections in 100 patients per year by treatment and risk profile. Additional risk factors are one or two of the following: age >60 years, chronic lung disease, chronic renal disease or high number of treatment failures; three risk factors: two of the above risk factors plus prior serious infections. DMARD, disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

Long Term:
The Effect of Biologics on Malignancy and Infection Risk



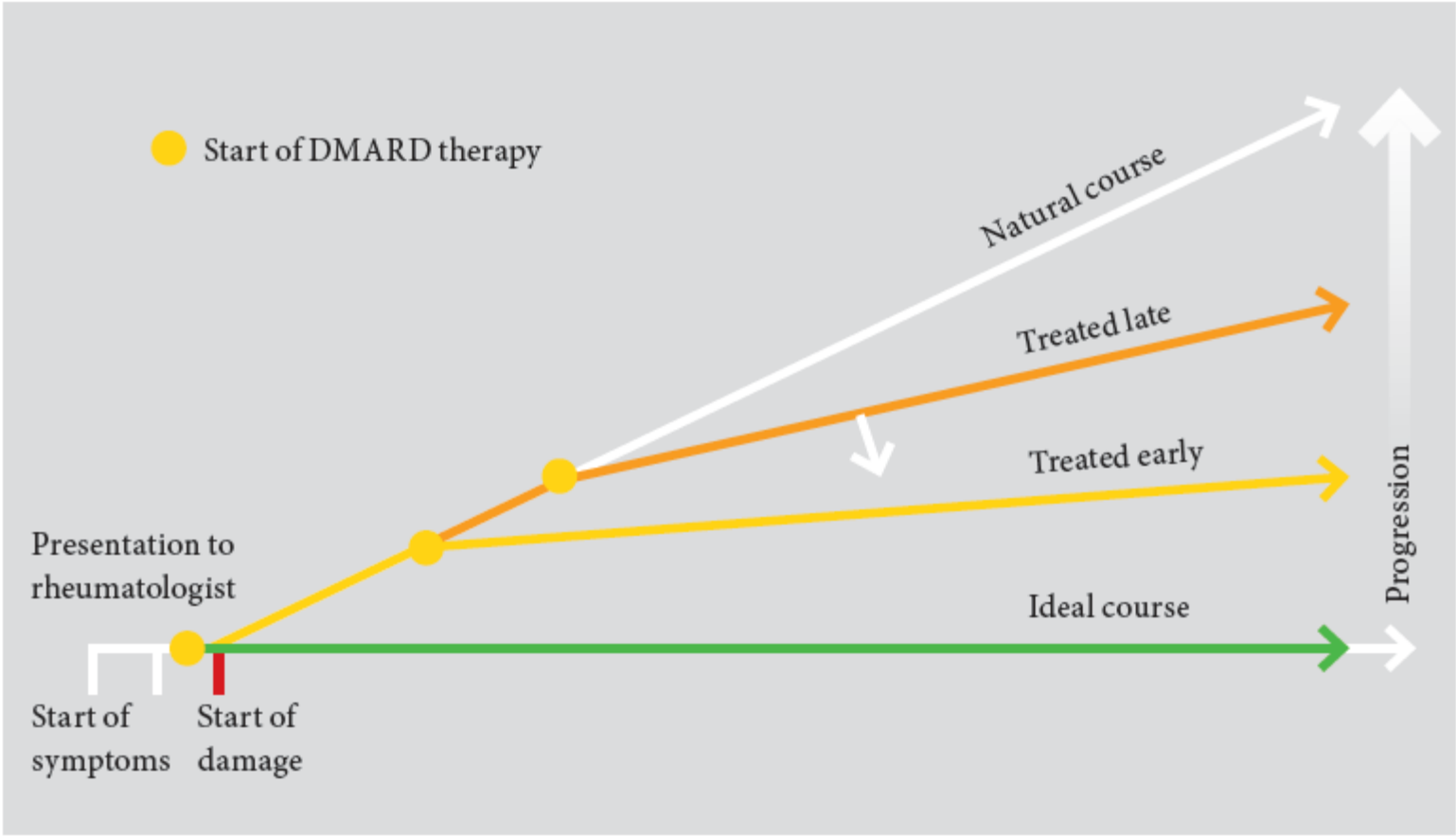


Figure 3.2 Altering the course of early rheumatoid arthritis. Untreated, most patients with rheumatoid arthritis (RA) will follow a course of progressive joint damage, increased morbidity, and mortality. Earlier treatment, however, has shown to alter this course. Ideally patients should be diagnosed at the earliest stages and disease-modifying antirheumatic drugs (DMARDs) commenced. Reproduced with permission from Breedveld and Kalden [18]©Sage.

What Causes RA?
(added to genetic risk)

CAN WE PREVENT RA?

Smoking

Being a Woman (who doesn't gets pregnant or take oral contraceptives)

Too Little Fish Oil

Too Much Dust

Too Little Alcohol

Periodontal Disease?

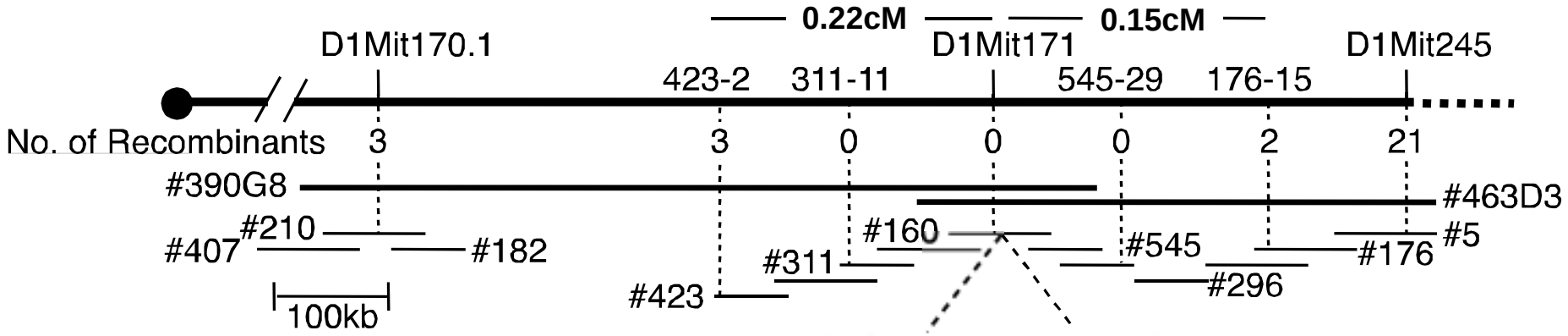
Certain Organisms?

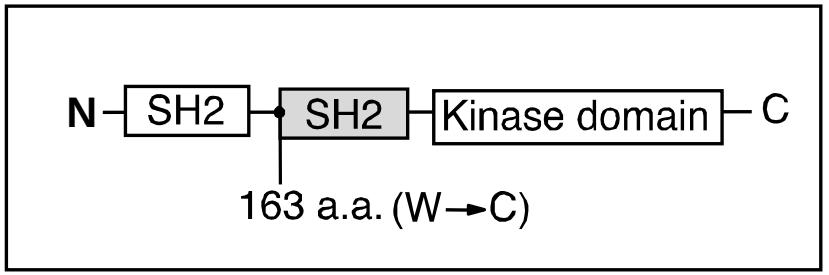
Adapted from Karlson and Deane, Rheum Dis Clin N Am 2012

4-mo-old SKG mouse

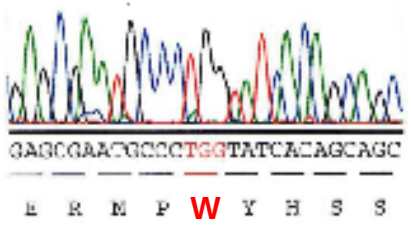
6-mo-old SKG mouse

A Mutation of the ZAP-70 Gene as the Cause of SKG Arthritis

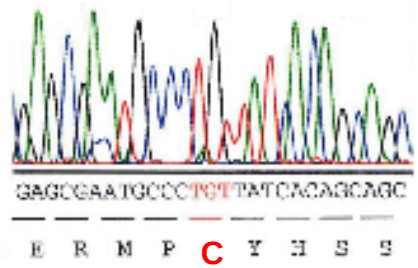




ZAP-70

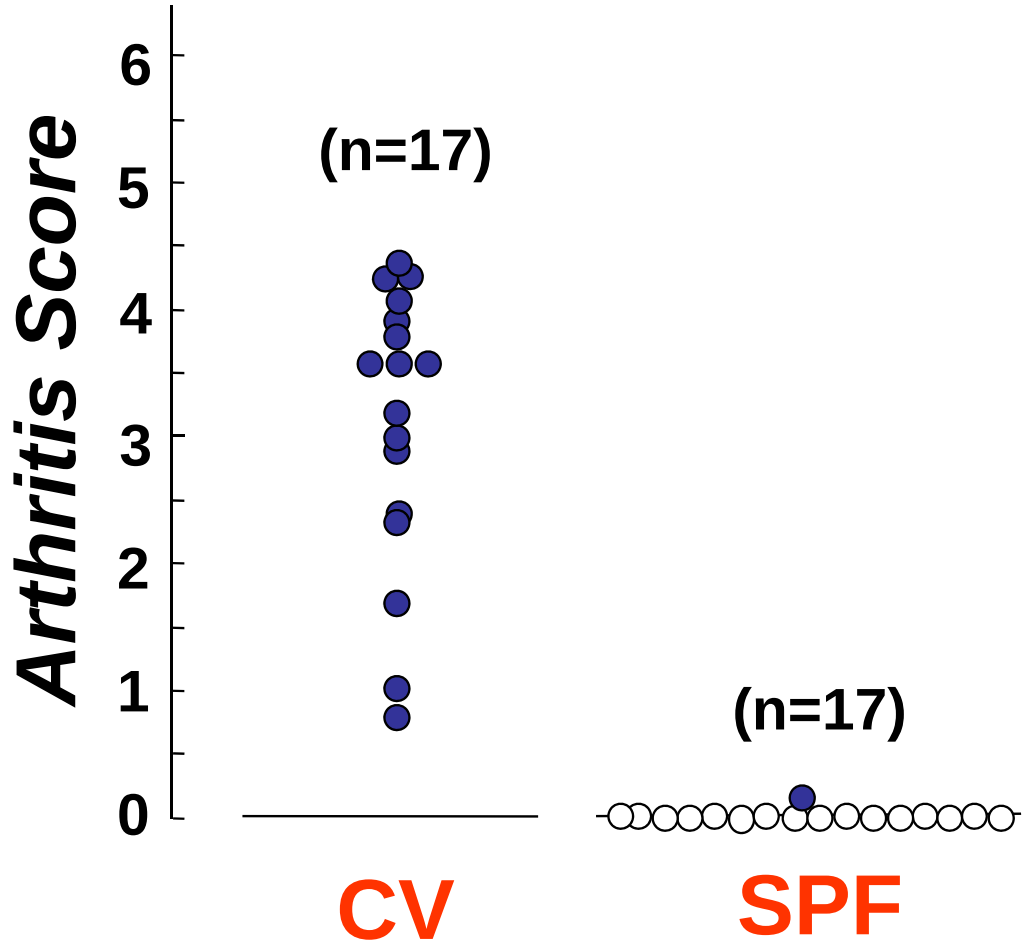


BALB/c



SKG

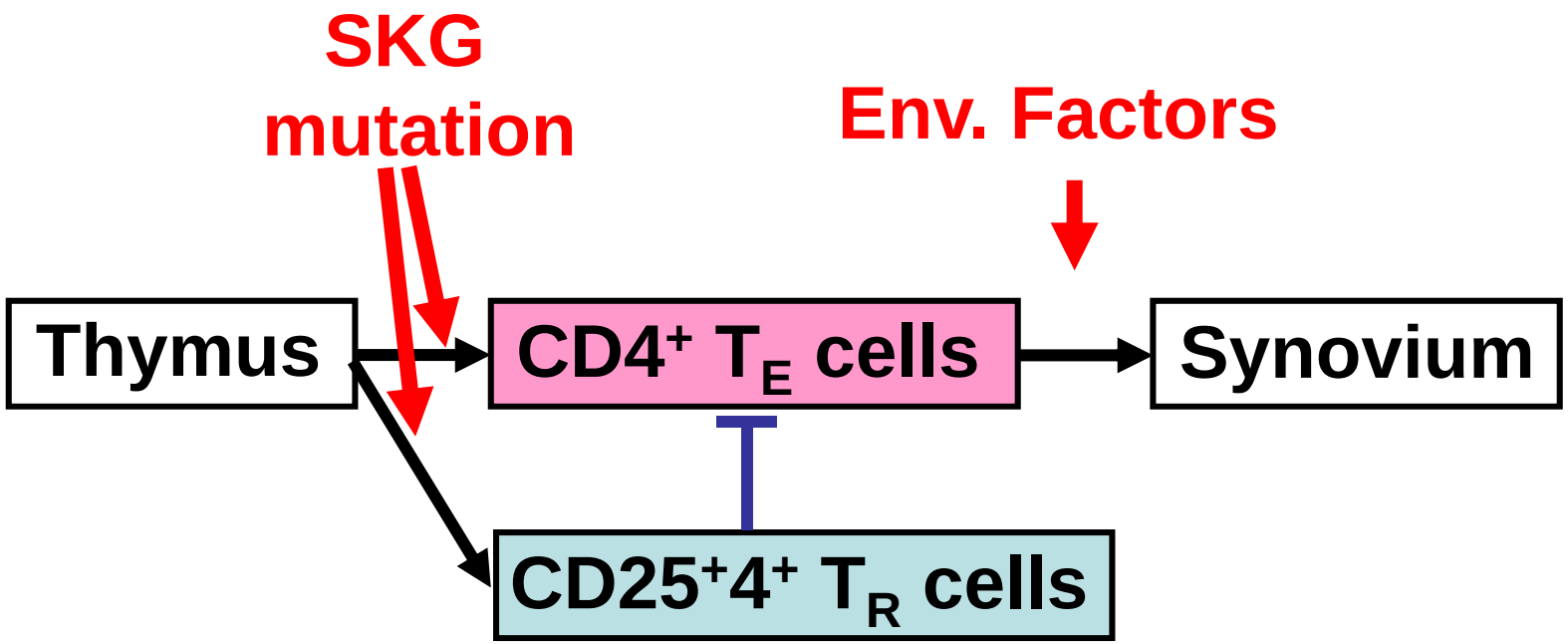
Failure of SKG Mice to Develop Arthritis in the SPF Condition



CV : Conventional Environment
SPF : Specific Pathogen-Free Environment

The Pathogenetic Mechanism of SKG Arthritis

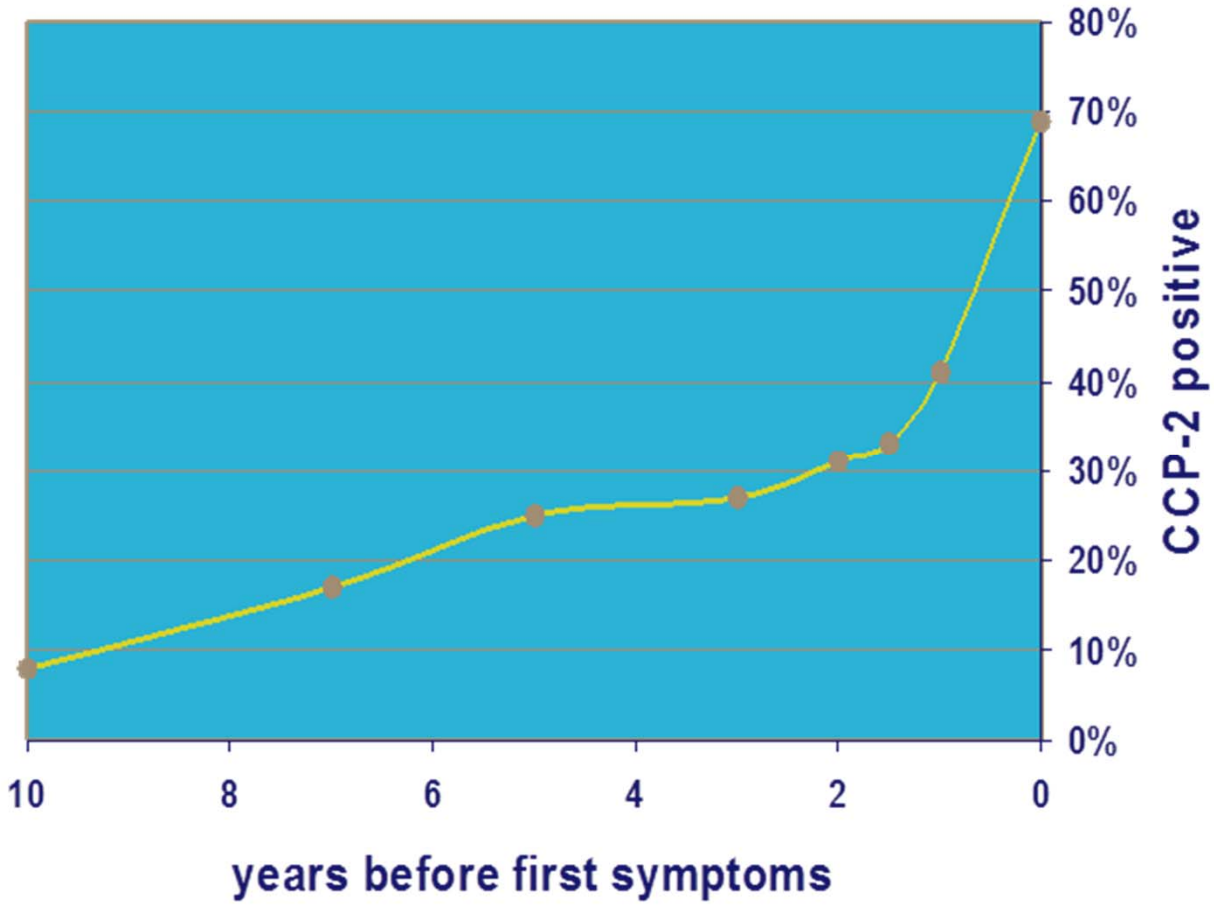
- **Thymic generation of arthritogenic T cells and their persistence in the periphery**
- **Activation of arthritogenic T cells by environmental agents through stimulating innate immunity**



Anti-CCP Before Clinical Onset of RA (Sweden)

83 early RA patients, all were former blood donors

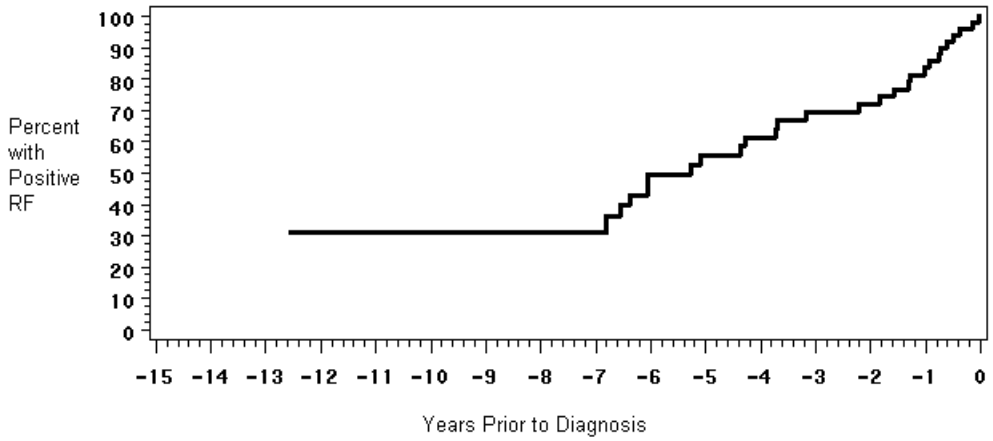
serum samples available from bloodbank from up to 10 years before onset of first symptoms



Rantapaa-Dahlqvist S, de Jong BA et al. Arthritis Rheum 2003; 48: 2741-9

Figure 1a. Timing of Appearance of Antibodies Prior to Diagnosis of Rheumatoid Arthritis

Median time of appearance of RF 5.3 years (95% CI 3.3, 6.8) prior to diagnosis



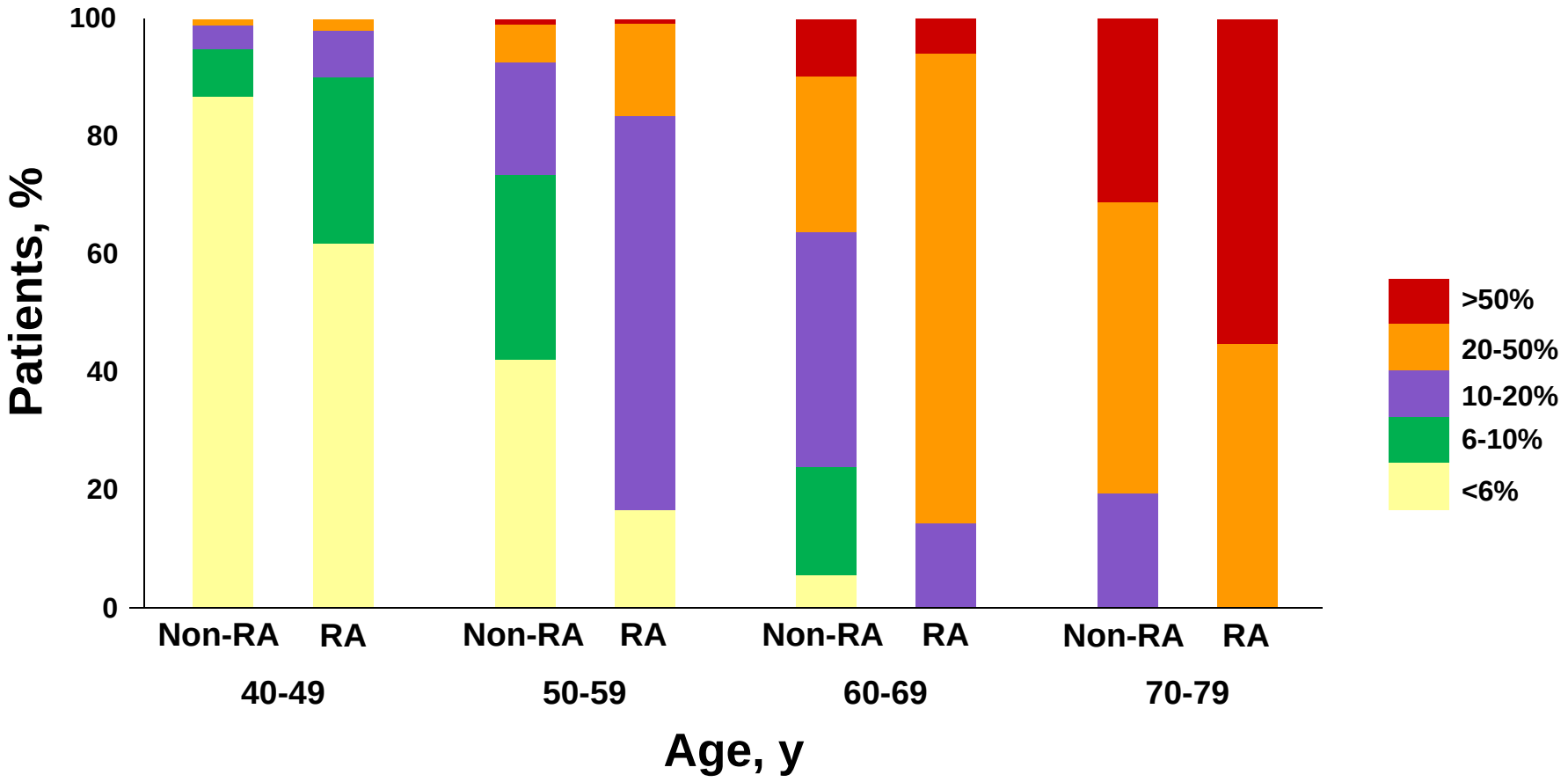
Risk of Rheumatoid Arthritis Varies Tremendously in Different Populations

- The North American RA estimate is .6%
- Most of the genetic risk is conferred by the “shared epitope - SE” encoding alleles of HLA-DRB1 which varies in frequency from 28 to 38%
- Several North American Native (NAN) populations have much higher rates of RA
    - 5.3% in the Pima of Arizona
    - 2.4% in the Tlingit of Alaska
- Cree/Objibway Central Canada NAN has SE frequencies as high as 60 to 95%

Cardiovascular Risk in RA – The New Therapeutic Frontier

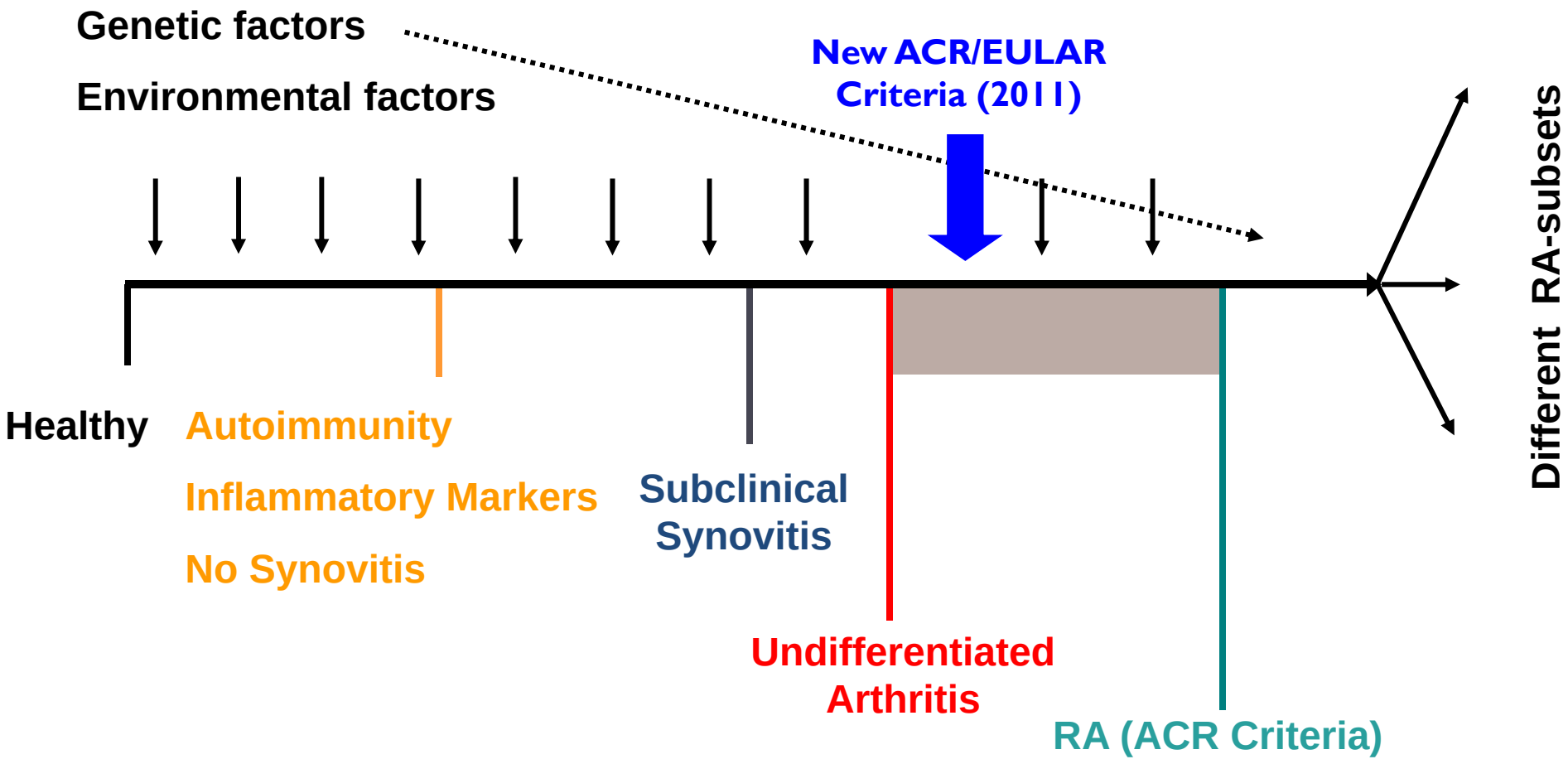
- Well known – 2-3% increased risk of CVD in RA in all age groups
- “Window of opportunity” - tight control of inflammation shortly after disease onset (within one year) attenuates CV risk
- Despite above, GC’s increase risk, especially in older onset RA

High 10-Year Risk of CVD in Newly-Diagnosed RA Patients



Adapted from Kremers HM, et al. *Arthritis Rheum.* 2008;58:2268-2274.

The Stages of RA



Van de Sande MG, et al. Ann Rheum Dis 2011;70:772–777

What is RA like in 2015?

Arthritis Care & Research
Vol. 67, No. 5, May 2015, pp 718–724
DOI 10.1002/acr.22497

BRIEF REPORT

Rheumatoid Arthritis is Associated With Higher Ninety-Day Hospital Readmission Rates Compared to Osteoarthritis After Hip or Knee Arthroplasty: A Cohort Study

JASVINDER A. SINGH,[1] MARIA C. S. INACIO,[2] ROBERT S. NAMBA,[3] AND ELIZABETH W. PAXTON[2]

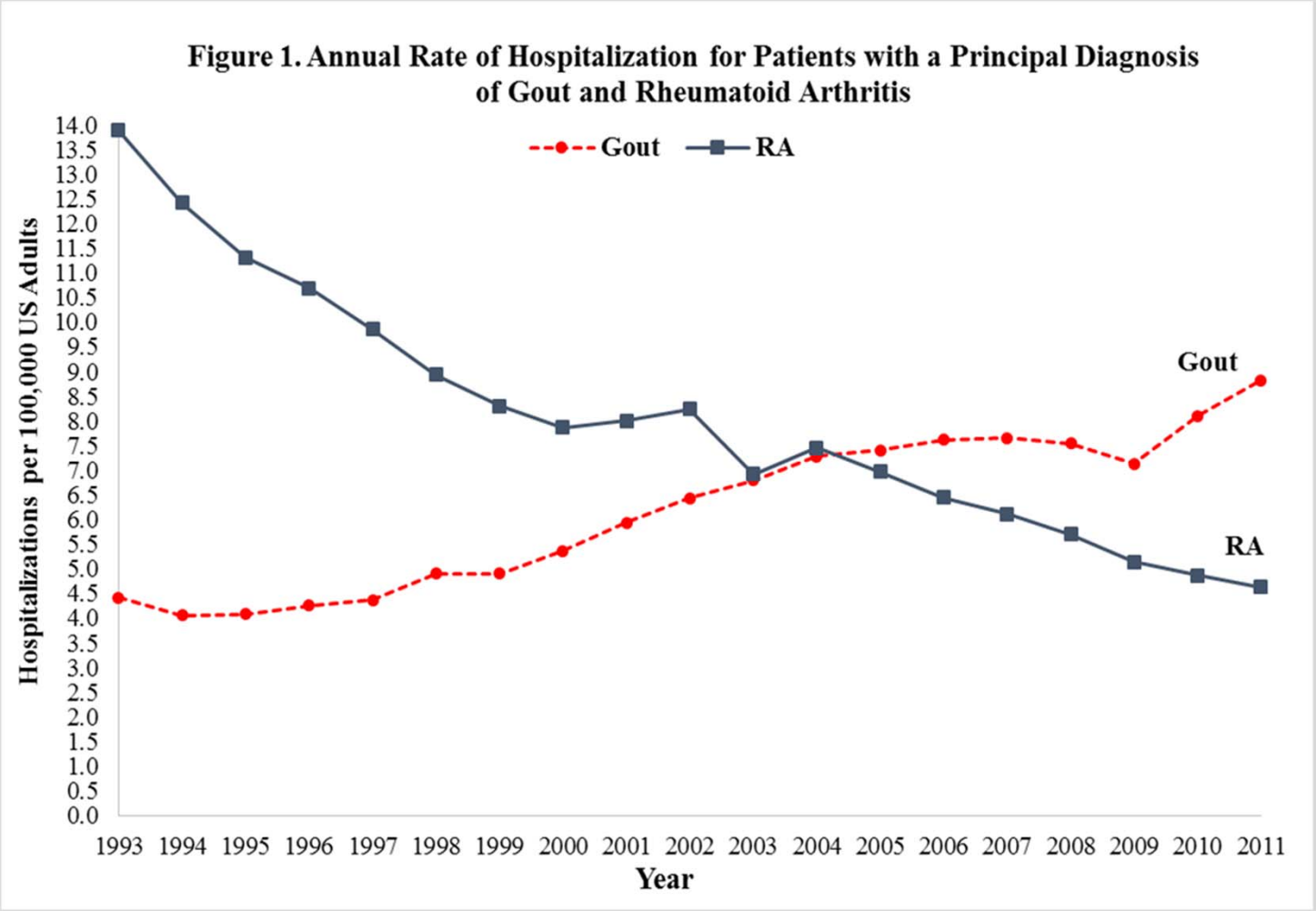
496/34,311 = 1.4%!!

Table 2. 90-day readmission rate for overall sample, primary indication for surgery, and operative year*

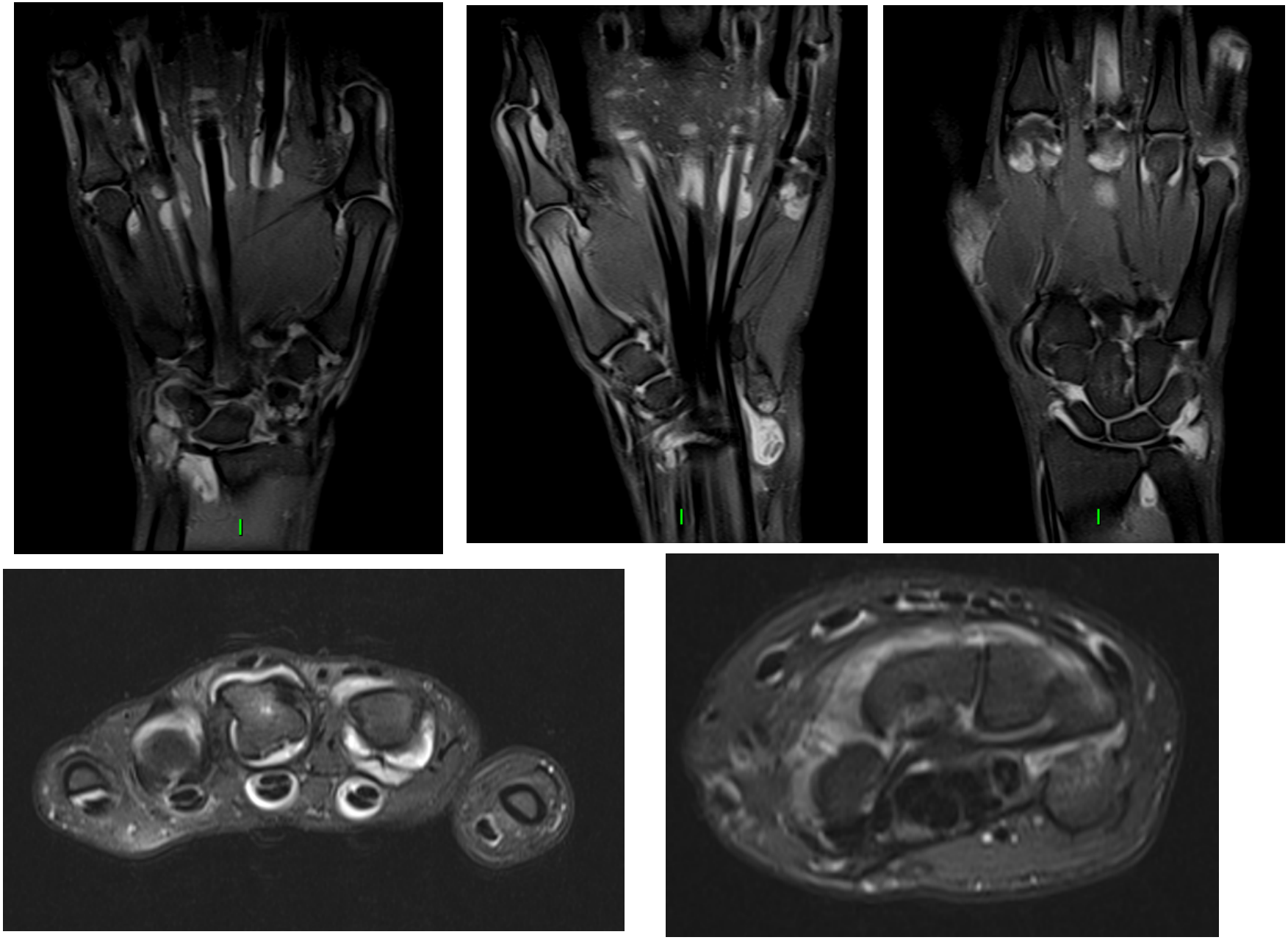
	Total (n = 34,311)	Osteoarthritis (n = 33,815)	Rheumatoid arthritis (n = 496)	*P*
Total	2,319 (6.8)	2,277 (6.7)	42 (8.5)	0.127
2009	734 (7.1)	687 (6.7)	9 (5.8)	0.640
2010	866 (7.4)	777 (6.7)	16 (8.9)	0.249
2011	916 (7.5)	813 (6.8)	17 (10.6)	0.055

* Values are the number (%), unless otherwise indicated.

Hospitalizations Due to Gout Have Increased



Choi, ACR Abstract, 2015.



Coronal and axial inversion recovery MR images of bilateral hands demonstrate synovitis and effusion of carpal and MCP joints as well as tenosynovitis of flexor tendons.

What is the main difference today?

1975

- Treating RA was like billiards compared to bowling
- We couldn't treat the disease; we managed the patient with RA
- We never used the "R" word

2015

- We treat the disease early and aggressively
- Yes, we even use the "R" word
- Today we are testing methods of disease prevention