BIOLOGIC DRUGS IN THE TREATMENT OF MYOSITIS

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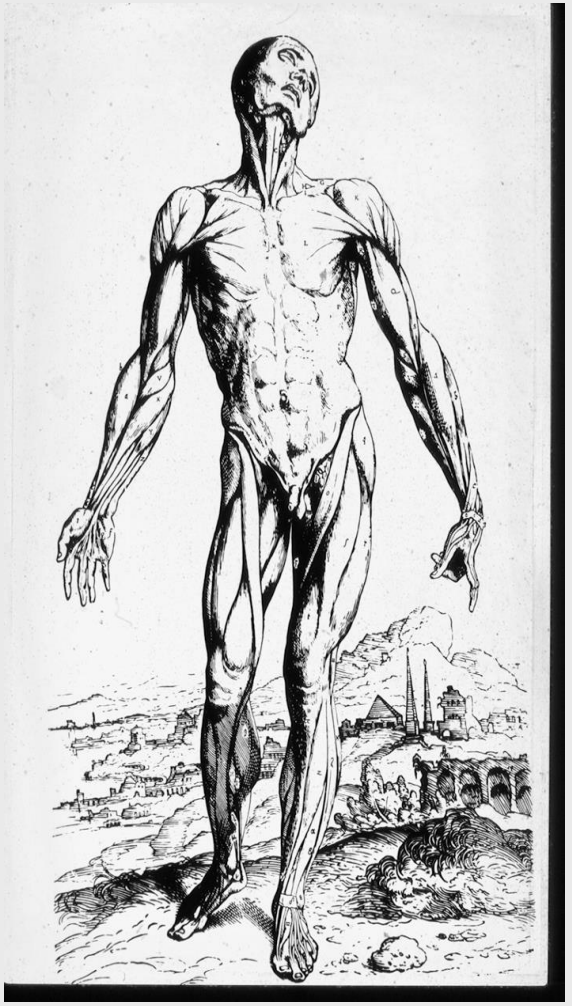


KEY FACTS – 1 -

- **Incidence of PM/DM/IBM 1.9-7.7 million**
- **Prevalence in the UK = 8/100,000**
- **Affects all ages but 2 peaks of onset; childhood onset 5-15 and adult onset 40-60. IBM peaks after 50 years.**
- **DM/PM overall F:M ratio = 2-3:1**

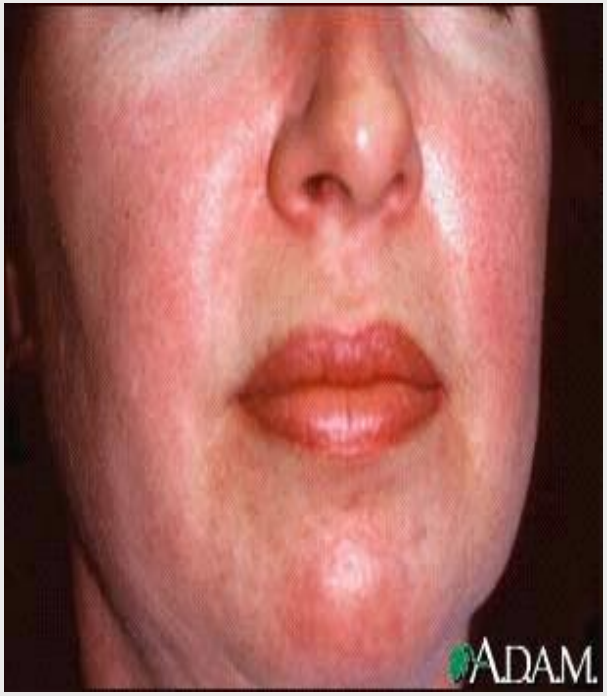
KEY FACTS – 2 – CLINICAL CLASSIFICATION

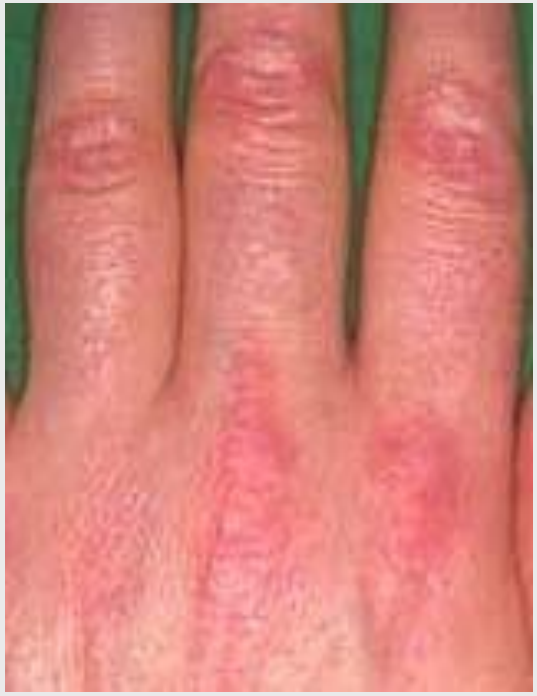
- **Adult onset idiopathic polymyositis**
- **Adult onset idiopathic dermatomyositis**
- **Childhood onset myositis (invariably dermatomyositis)**
- **Myositis associated with other autoimmune rheumatic disease**
- **Inclusion body myositis**
- **Rare forms: focal, ocular, eosinophilic, granulomatous myositis**
- **Cancer associated myositis**

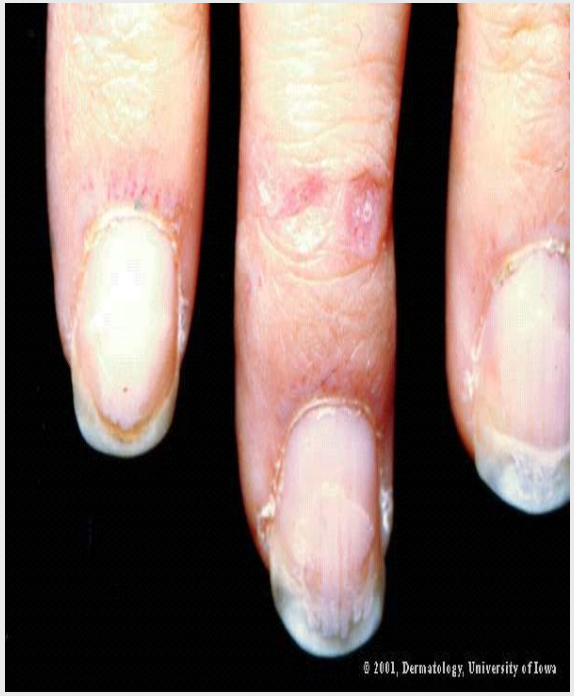
KEY FACTS – 3 – A MULTISYSTEM DISEASE

- **Constitutional – fever, wt loss, nodes, fatigue**
- **Joints – arthralgia, arthritis**
- **Gastrointestinal – dysphagia, abdo pain**
- **Cardiovascular – palpitations, chest pain**

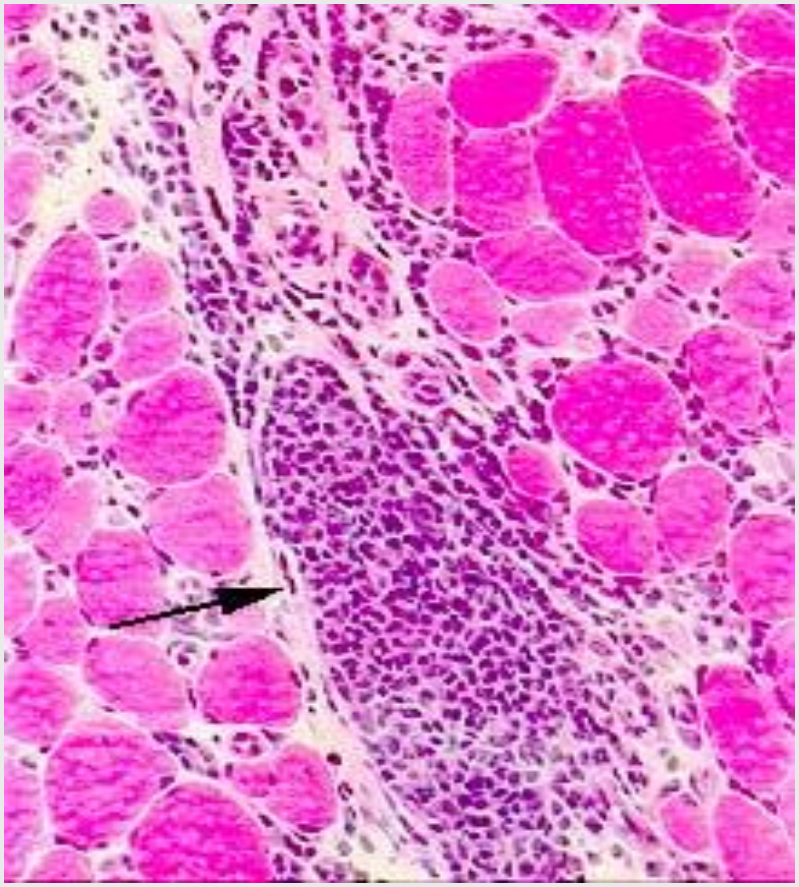
SKIN – RASHES, ERYTHEMA, ULCERATION AND ERYTHRODERMA

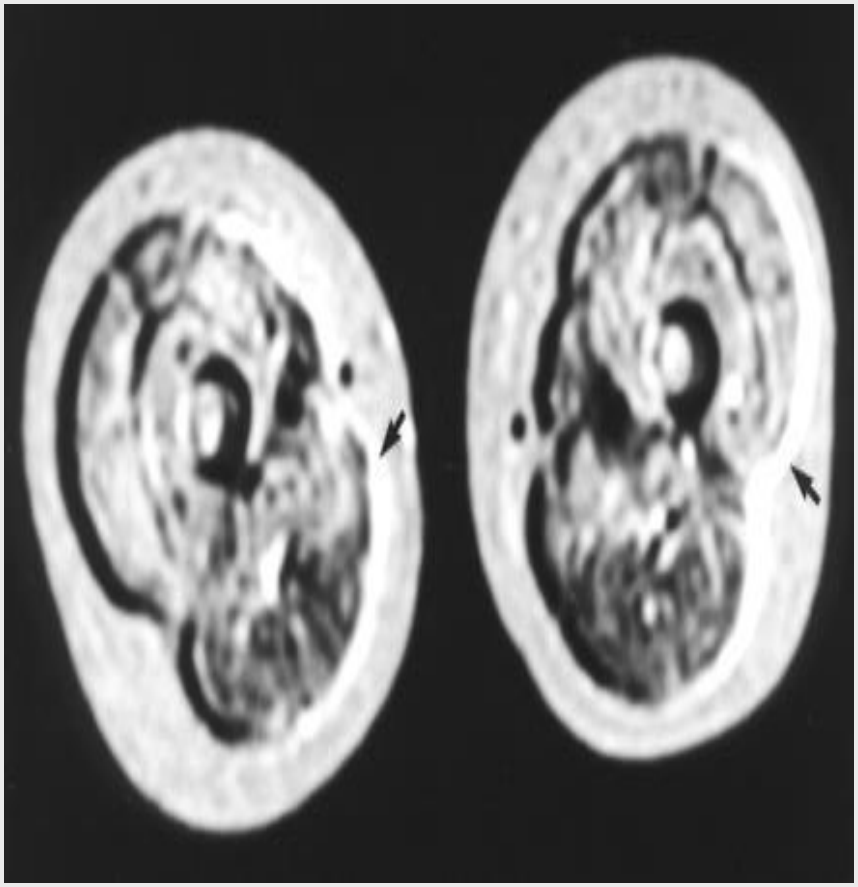




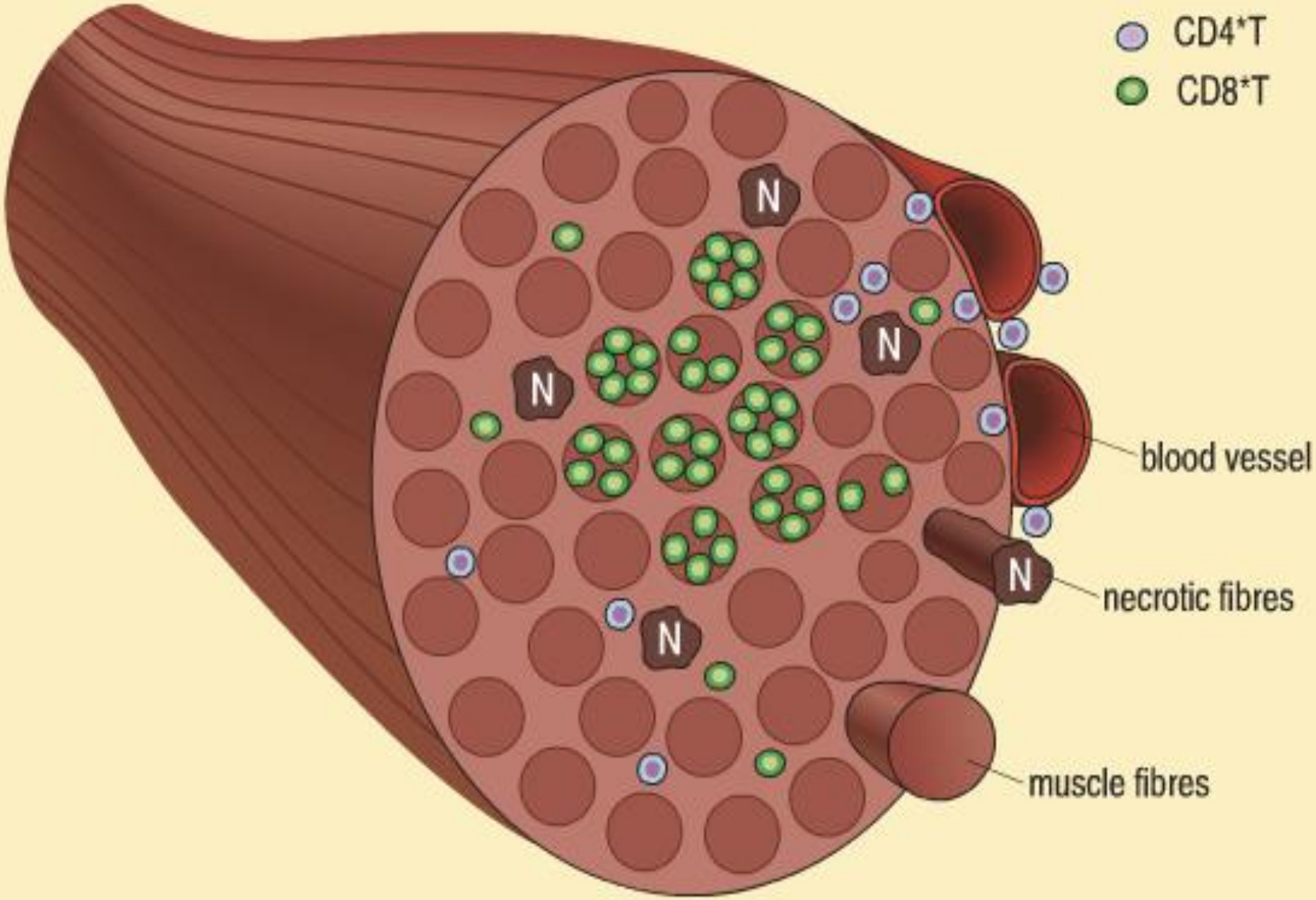


MUSCLE – MYALGIA, WEAKNESS

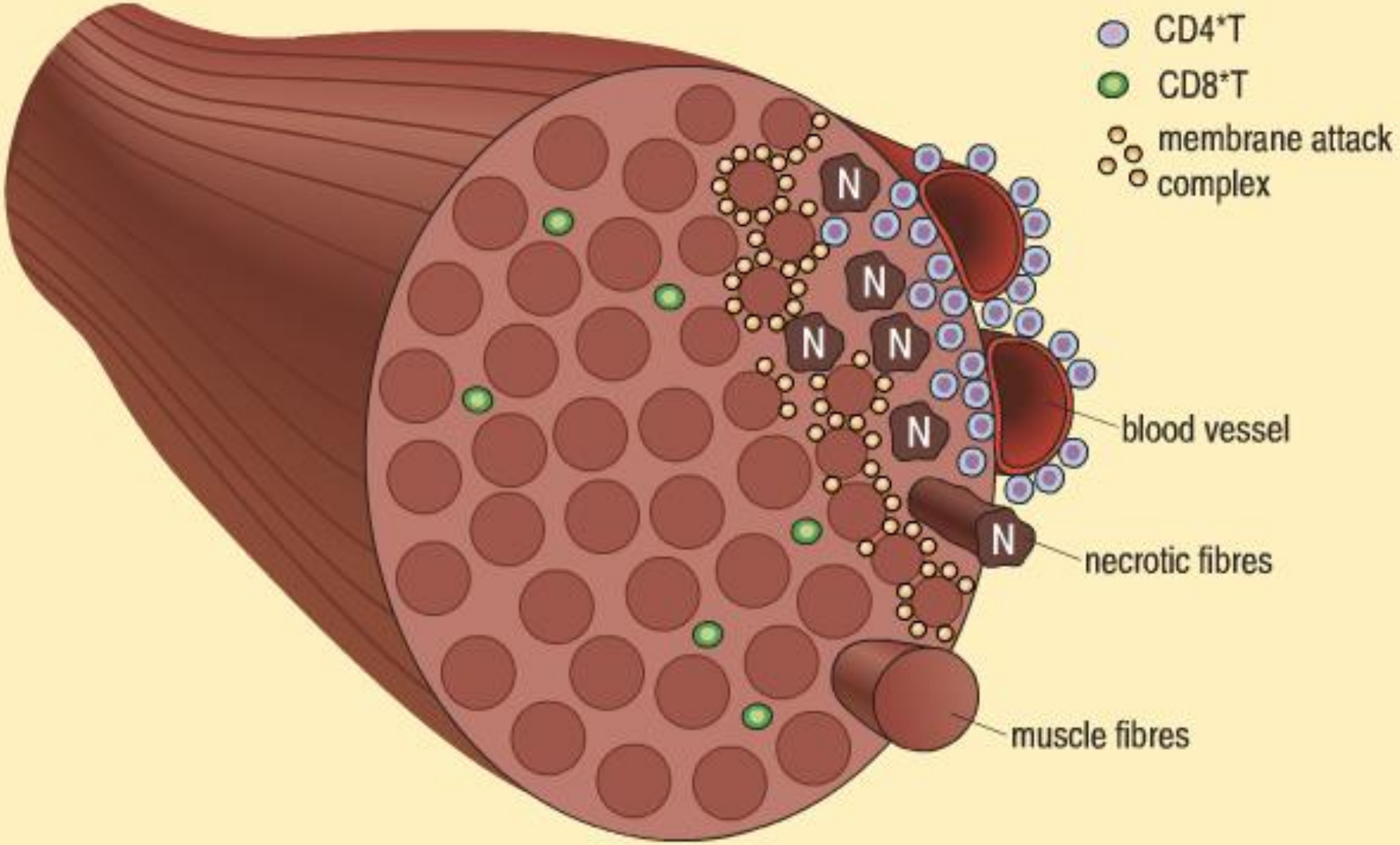




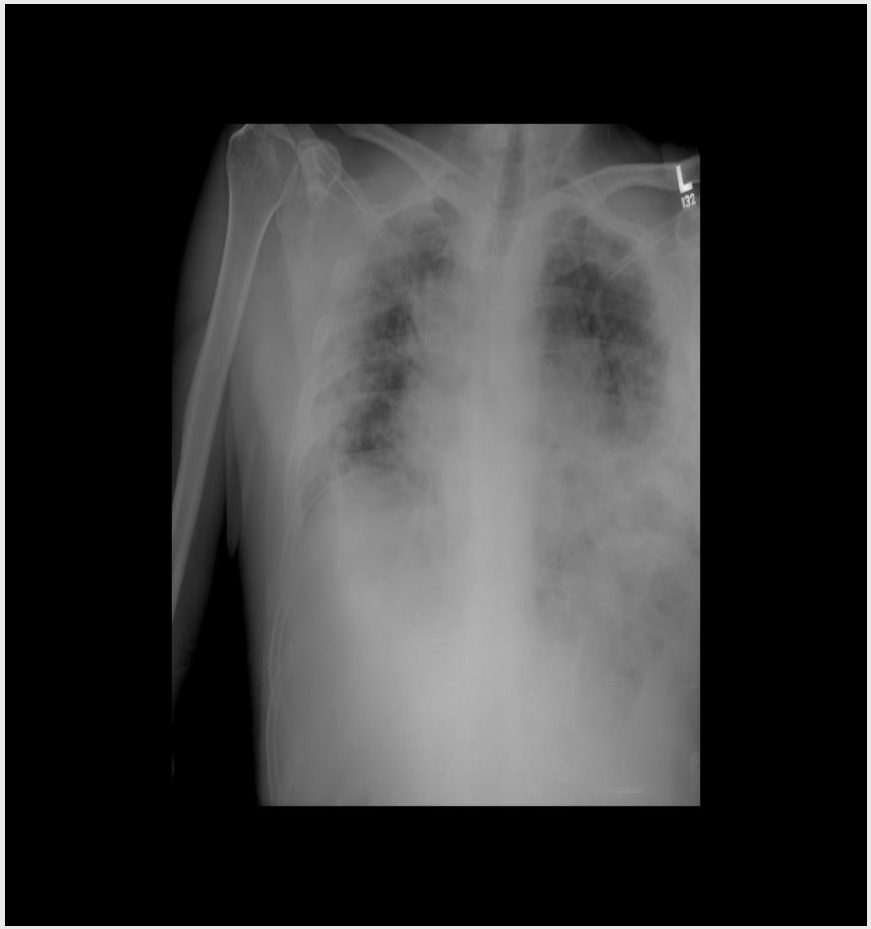
Polymyositis: histopathological features

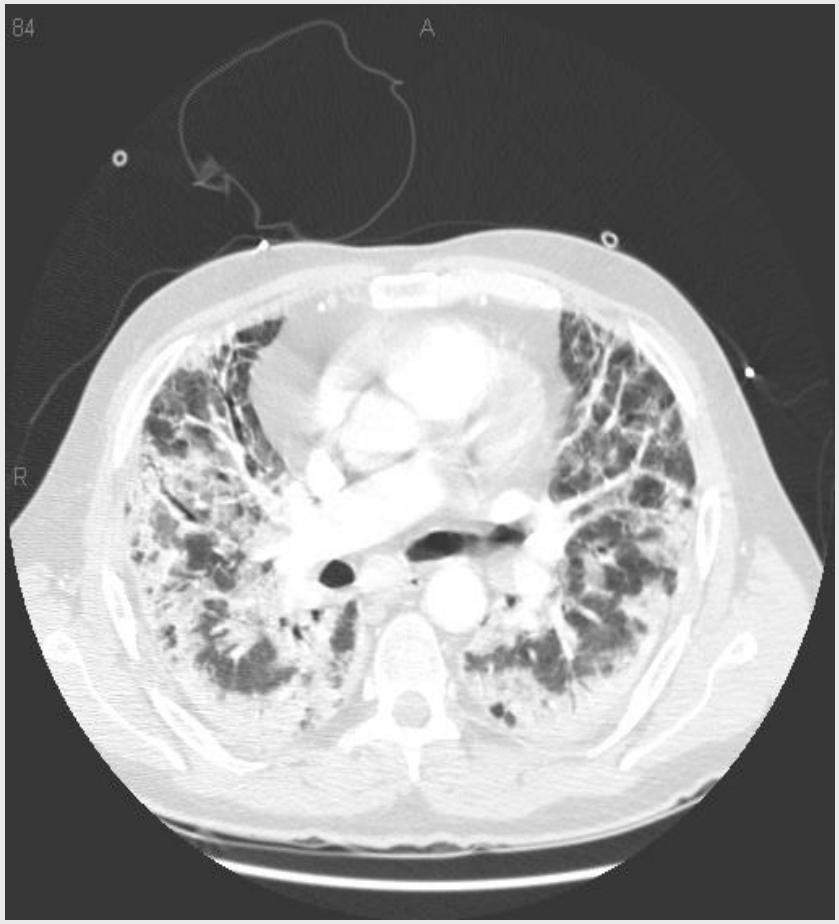


Dermatomyositis: histopathological features



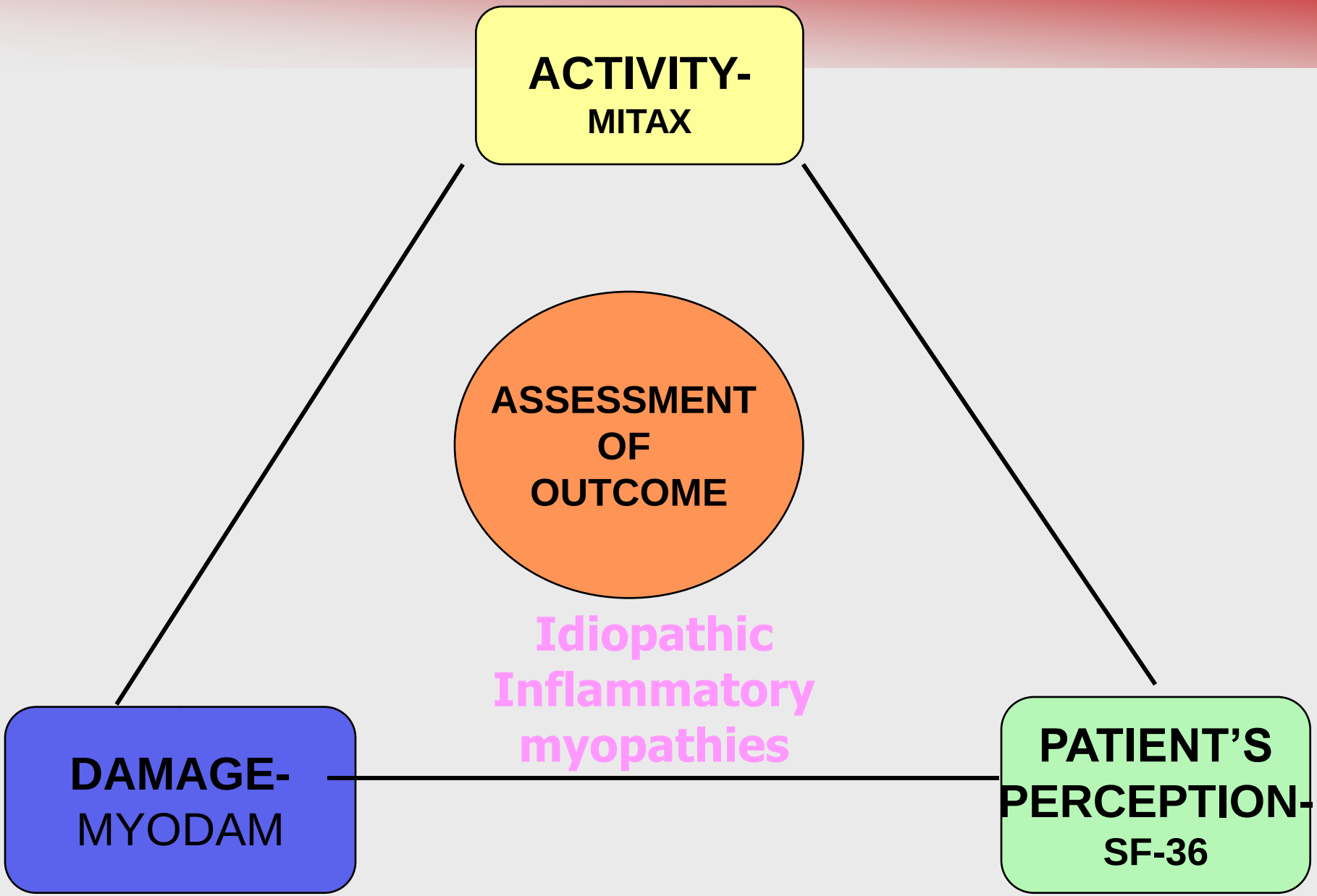
Respiratory – dysphonia, dyspnoea





TRADITIONAL METHODS OF ASSESSING MYOSITIS

- Clinical
- Enzymes
- EMG
- Biopsy


ACTIVITY-
MITAX
ASSESSMENT
OF
OUTCOME
Idiopathic
Inflammatory
myopathies
DAMAGE-
MYODAM
PATIENT'S
PERCEPTION-
SF-36

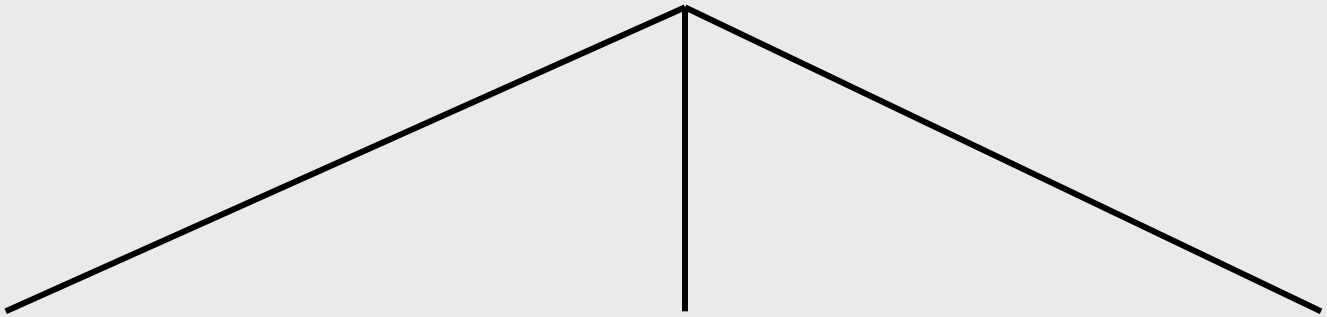
CURRENT ASSESSMENT OF MYOSITIS – 1 -

	Activity	Damage
Clinical	rash, arthritis, fever, MMT, myalgia	Atrophy, contractures
Laboratory	↑ Muscle enzymes (CK, LDH, AST, ALT)	↓ Creatinine, normal enzymes
Systemic	RFTs, HRCT, barium swallow	RFTs, HRCT, barium swallow
EMG	↑ fibrillations	normal
Biopsy	Inflammatory cells, necrosis, MHC staining	Little cells, atrophy, fibrotic tissue
MRI	↑ signal suggesting inflammation	Fat replacement, atrophy

THE UCL EXPERIENCE – 1 -

- **Retrospective study (1976 → 2013)**

- **97 patients followed up during this period (72F, 25M)**



	Adult-onset Polymyositis [APM]	**Adult-onset dermatomyositis [ADM]**	**Overlap syndrome [OS]**
n =	**35**	**37**	**25**

THE UCL EXPERIENCE – 2 -

	All Patients	Those Who Died
	n = 97	n = 24
	%	%
ADM	38	37
APM	36	33
OS	26	29
Female	74	58
Male	26	42
Caucasian	64	67
Afro-Caribbean	21	21
South Asian	10	8

THE UCL EXPERIENCE – 3-

	All Patients	Those Who Died
	n = 97	n = 24
Age at Diagnosis	41 years	42 years
Median Duration of Symptoms (IQR)	6 (9)	6 (5.5)
Highest CK		
< 2 X ULN	3%	0%
> 10 x ULN	63%	67%
ANA +ve	49%	58%

THE UCL EXPERIENCE – 4-

	All Patients	Those Who Died
	n = 97	n = 24
	%	%
Cardiac involvement	25	50
Lung involvement	32	46
Malignancy	12	25
Infection	33	58

THE UCL EXPERIENCE – 5 -

	All Patients	Those Who Died
	n = 97	n = 24
Treatment	%	%
Steroids	7	12
Steroids + 1 IS	27	16
Steroids + 2 IS	26	33
Steroids + 3 IS	11	16
Steroids + 4 or more IS	29	21
Disease Course		
Monophasic	36	25
Relapsing/remitting	34	33
Chronic Persistent	30	42

THE UCL EXPERIENCE – 6 -

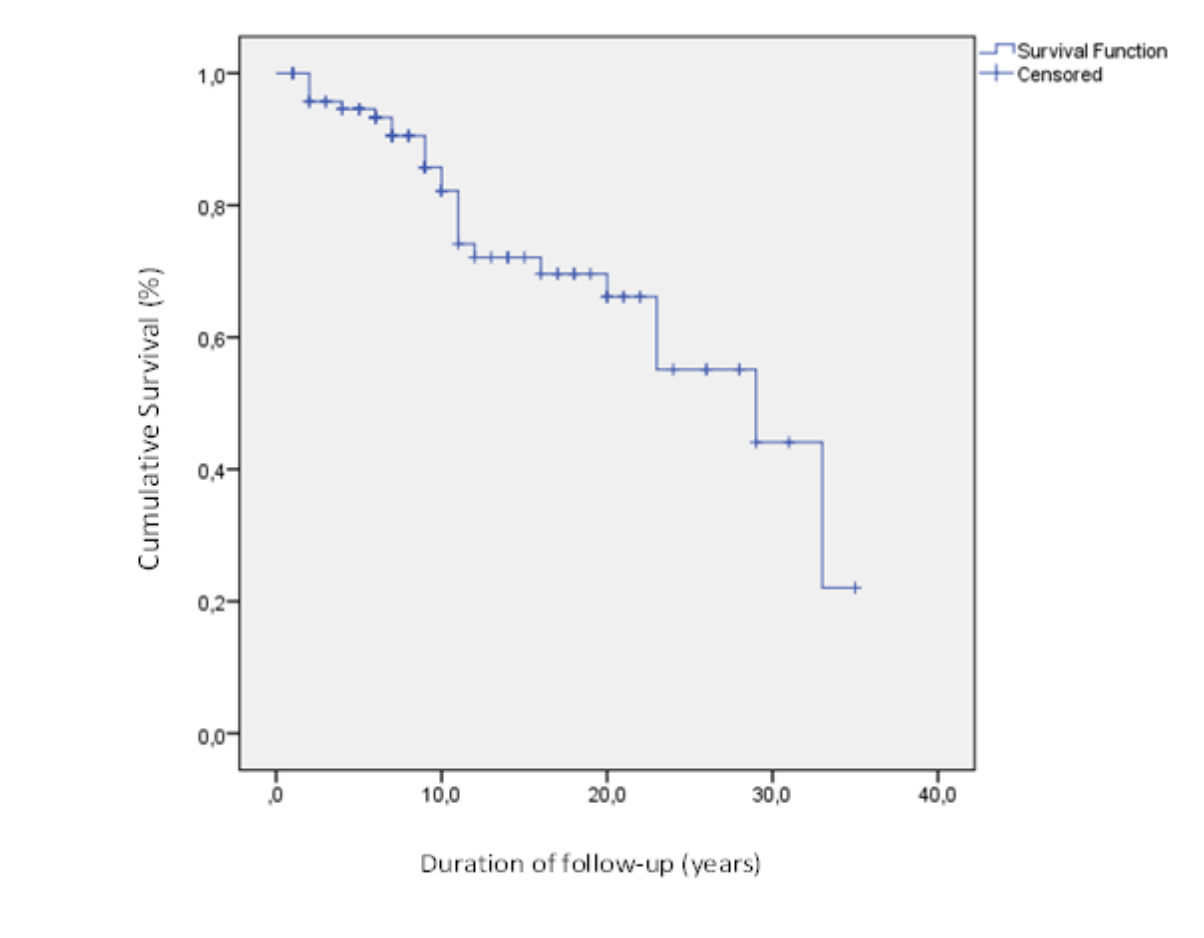
Statistically significant factors associated with ↓survival

Univariate Analysis	Hazards Ratio	Confidence Interval	p =
Lung Involvement	1.78; 95%	1.13 – 2.82	0.013
Infection	4.18; 95%	1.61 – 10.91	0.003
Upper and Lower Limb Involvement	0.13; 95%	0.03 – 0.62	0.010
Multivariate Analysis			
Infection	3.68; 95%	1.38 – 9.82	0.009
Upper and Lower Limb Involvement	0.16; 95%	0.03 – 0.81	0.027

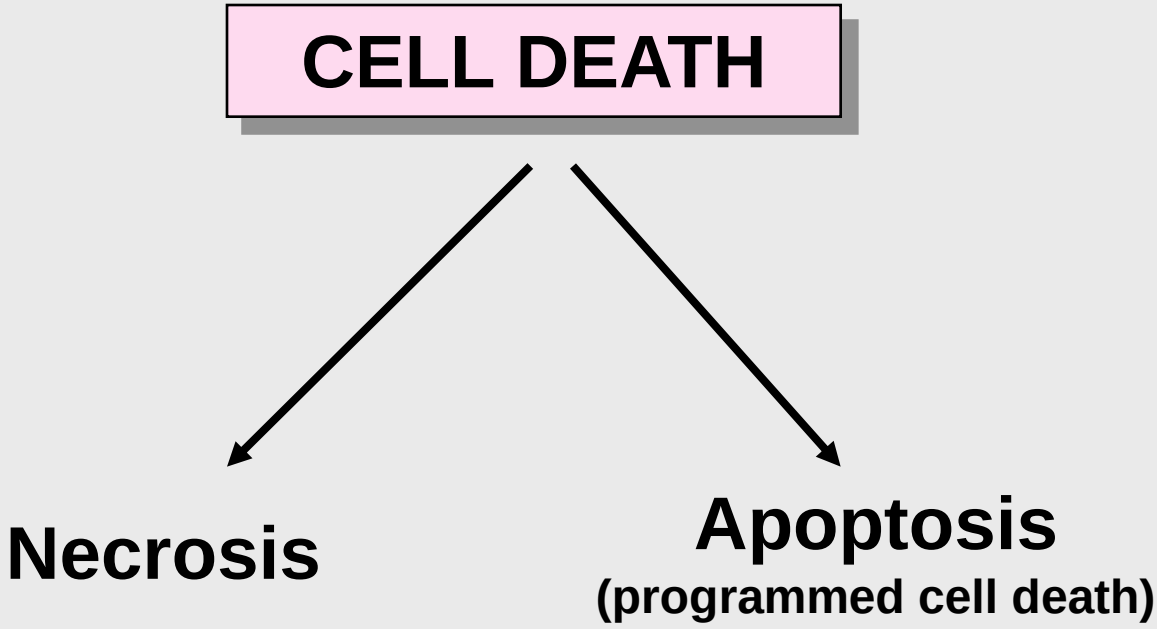
THE UCL EXPERIENCE – 7 -

Causes Of Deaths	n =
Lung	2
Cardiac	4
Malignancy	6
Infection	7
Other:-	
Trauma	1
GI bleeding	1
Uncertain	3

OUTCOME UCL MYOSITIS COHORT (1979 – 2015)
n = 97



CELL DEATH

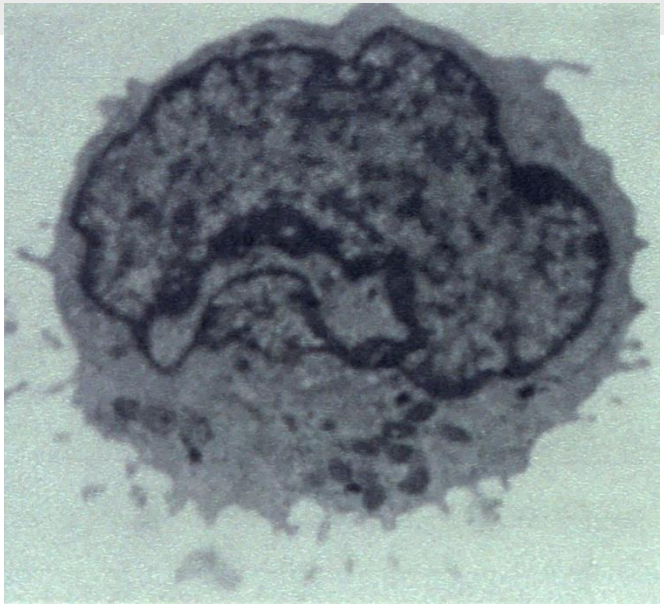


APOPTOSIS - HISTORY

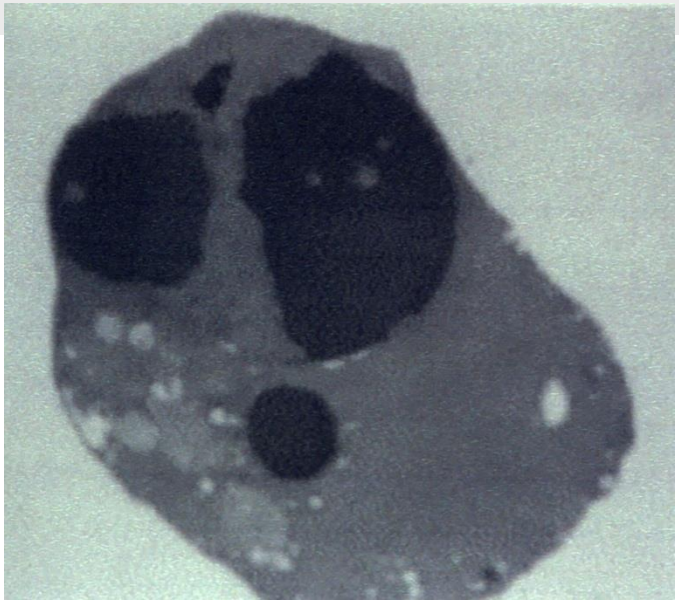
- First observed histochemically by Kerr (Australia) in 1965
- Was referred to as ‘shrinking necrosis’ in 1971
- ‘Apoptosis’ first used in 1972
- Now thought to be the major mechanism of normal cell death in complex organs
- Characterised by an orderly sequence of well-defined biochemical events

MORPHOLOGY OF APOPTOSIS

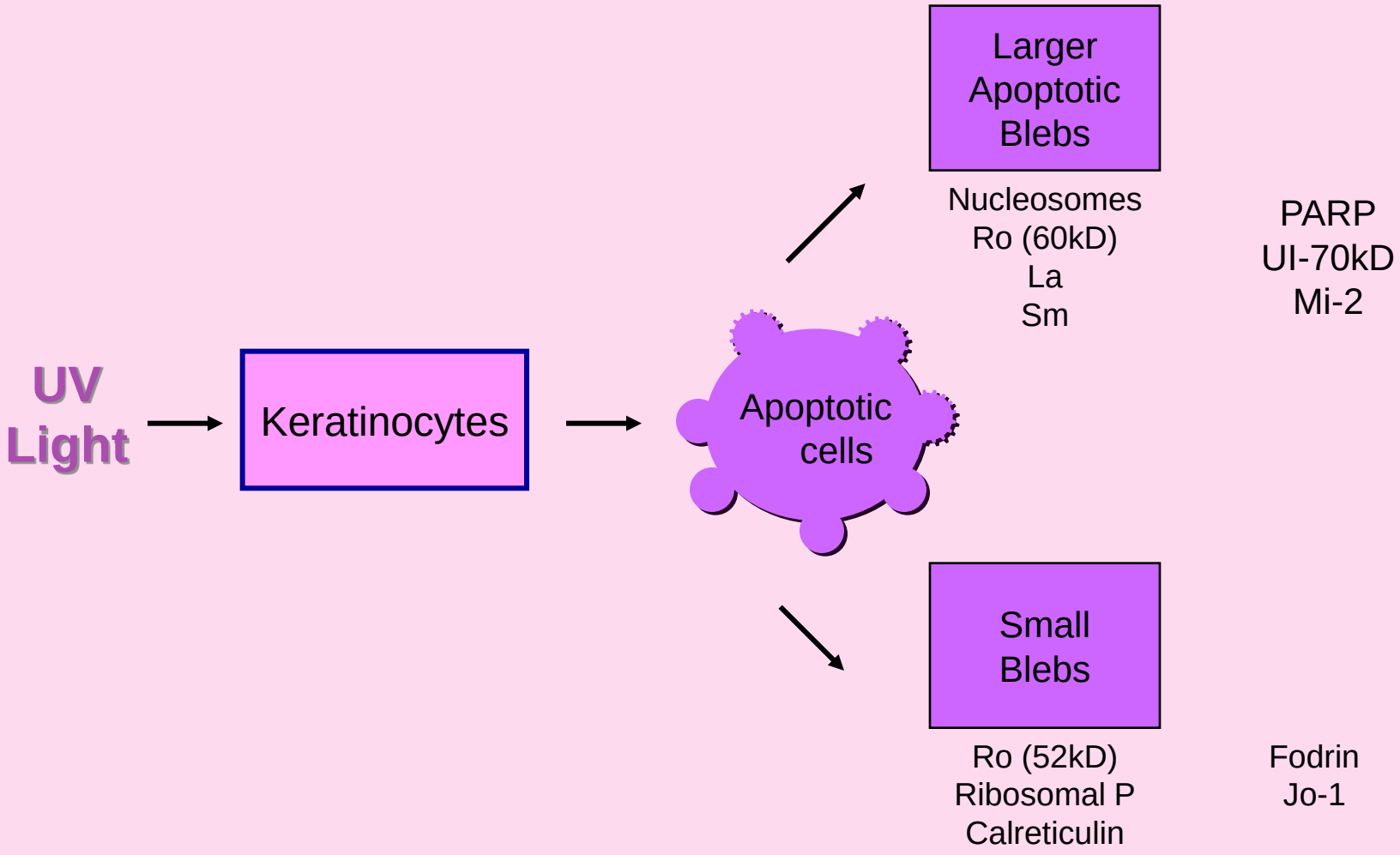
Viable cell



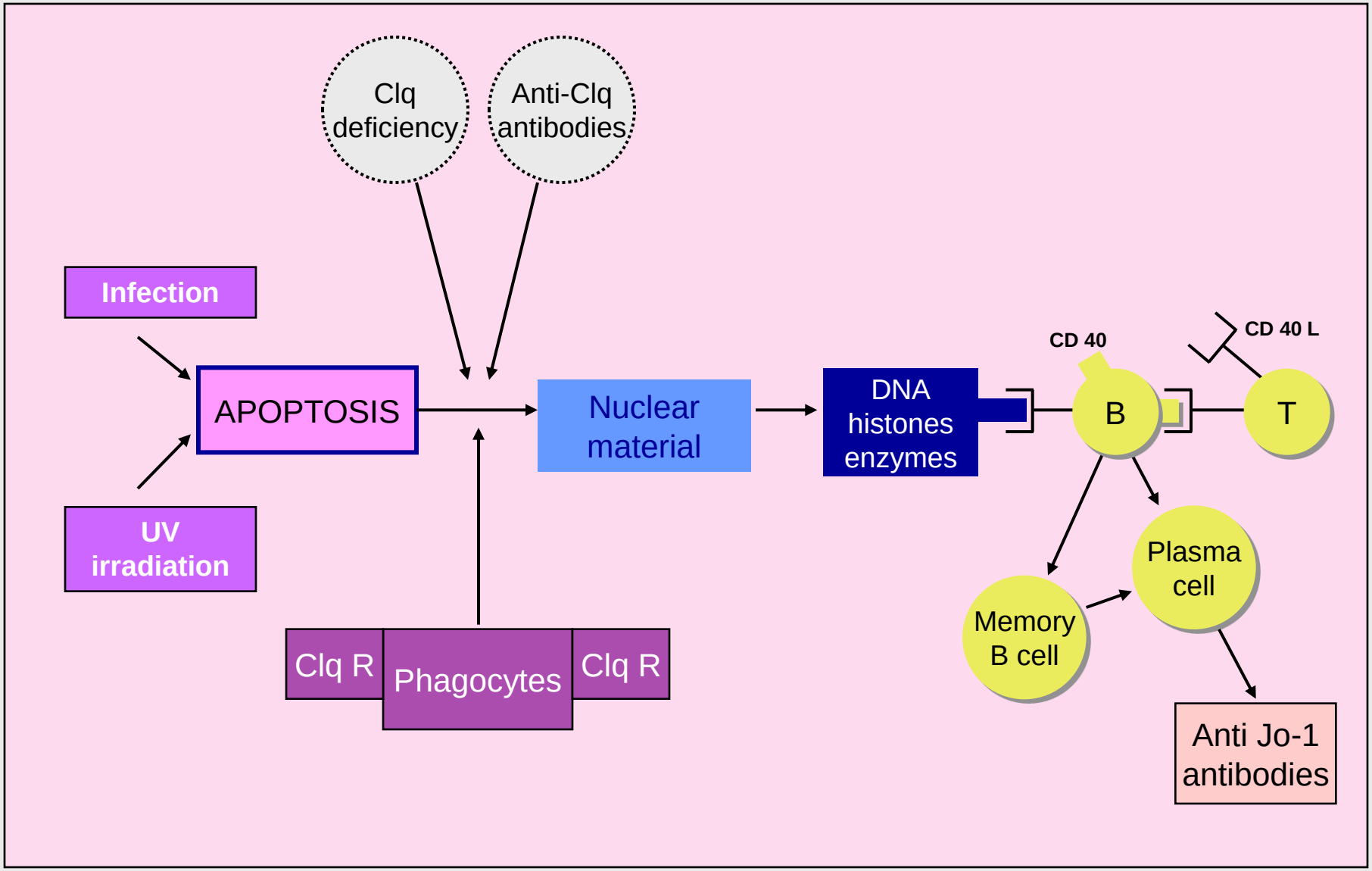
Apoptosis



CELL DEATH


Larger Apoptotic Blebs
Nucleosomes
Ro (60kD)
La
Sm
PARP
UI-70kD
Mi-2
UV Light
Keratinocytes
Apoptotic cells
Small Blebs
Ro (52kD)
Ribosomal P
Calreticulin
Fodrin
Jo-1

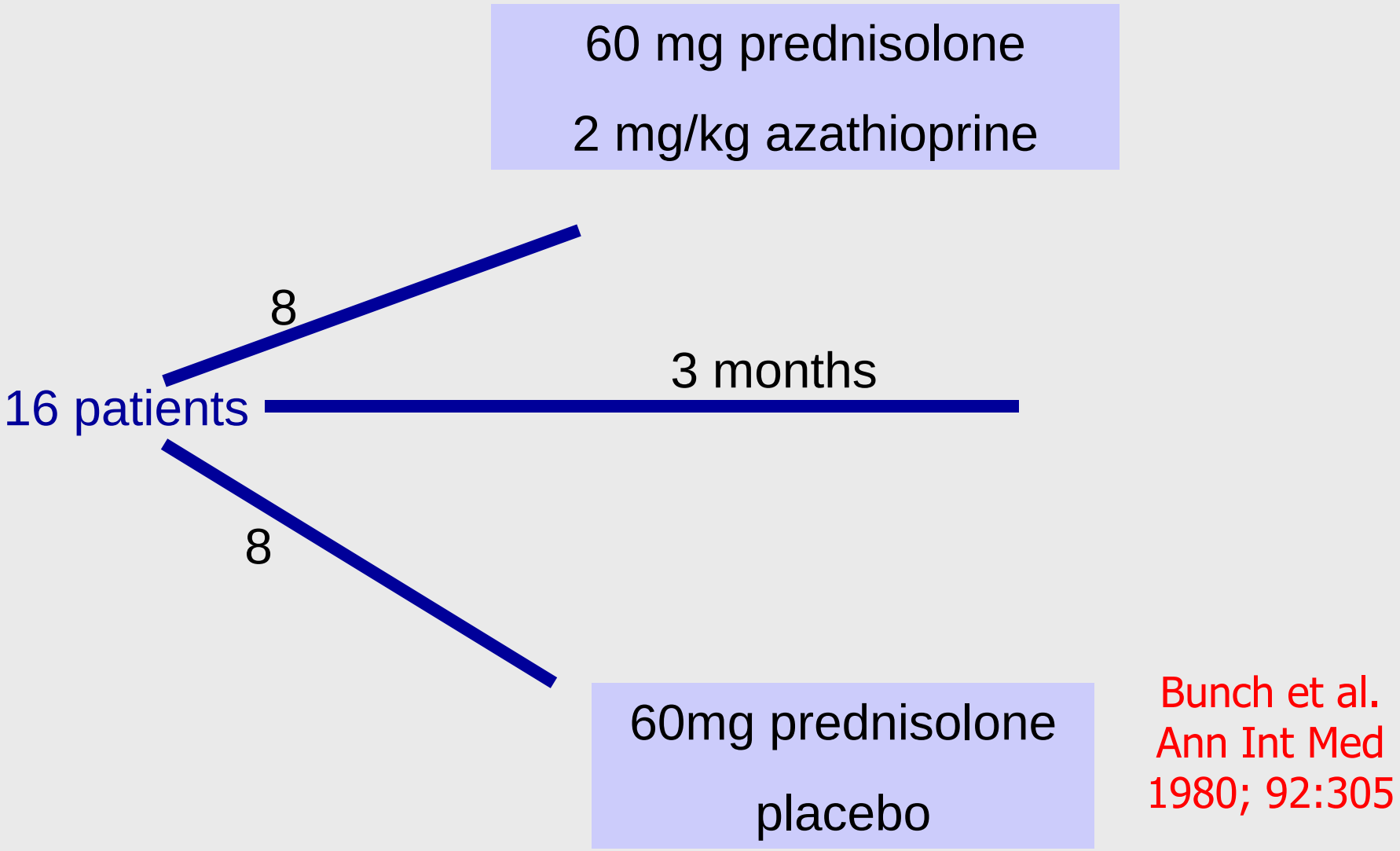
CELL DEATH


Clq deficiency
Anti-Clq antibodies
Infection
UV irradiation
APOPTOSIS
Nuclear material
DNA histones enzymes
CD 40
CD 40 L
B
T
Plasma cell
Memory B cell
Anti Jo-1 antibodies
Clq R
Phagocytes
Clq R

CORTICOSTEROIDS AND MYOSITIS

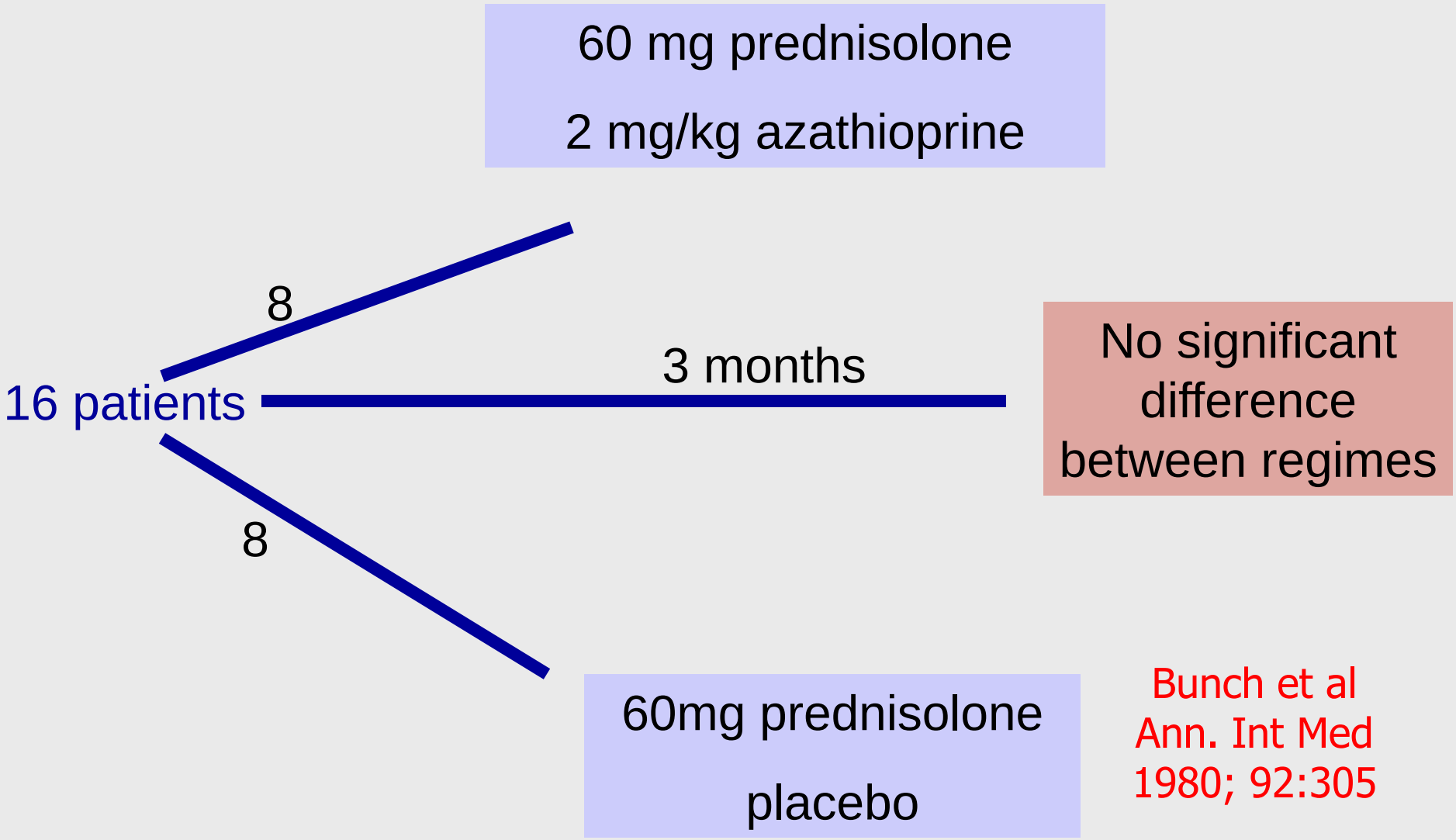
- Have never been tested adequately in randomised, placebo-controlled trials
- *Carpenter (1977)* compared 20 mg + prednisolone vs < 10 mg /day over an 8 week period
- Most authors have suggested a starting dose of 1-2 mg/kg prednisolone but this has never been validated
- Efforts have been made to show that lower doses (0.5 mg/kg)mg may be sufficient e.g. *Nzeusseu et al. Clin Exp Rheum 1999; 17,441-6.*

IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS (DOUBLE-BLIND PROSPECTIVE TRIAL)



Bunch et al.
Ann Int Med
1980; 92:305

IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS (DOUBLE-BLIND PROSPECTIVE TRIAL)



Bunch et al
Ann. Int Med
1980; 92:305

IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS (DOUBLE-BLIND PROSPECTIVE TRIAL)

Followed by an open 3 year study

CONCLUSIONS

‘the distinct impression one perceived at the end of the 3 years was that the group on azathioprine was stronger and required less prednisolone than the group on prednisolone alone’

Bunch. A & R; 1981: 24-45

IMMUNOSUPPRESSIVES (AZATHIOPRINE) AND STEROIDS

- Of 25 patients with steroid resistant myositis given oral methotrexate 88% had significant disease improvements and 43% reduced their steroids.

  Bohan et al. Medicine 1977; 56:25

- A randomised control trial in 36 patients of methotrexate and cyclosporin A showed equivalent clinical improvement and decreased CK.

  Venkovsky et al. Scand J Rheum 2000; 29:95

IMMUNOSUPPRESSIVES

In a randomised trial of 30 patients with treatment resistant myositis an intention to treat analysis showed a trend to improvement ($p=0.025$) for those given oral azathioprine and methotrexate compared to IV methotrexate.

Villaba et al. A & R 1998; 41: 392

IVIG AND MYOSITIS

- Several cases reports suggesting benefit
- In a double blind placebo-controlled trial of 15 patients, 8 given IVIg (and continuing oral prednisolone) showed significant improvement in muscle strength ($p < 0.018$) and symptoms
- ($p < 0.035$) whereas the 7 given the placebo showed no benefit.
  - Dalakas et al. N Engl J Med 1993; 32

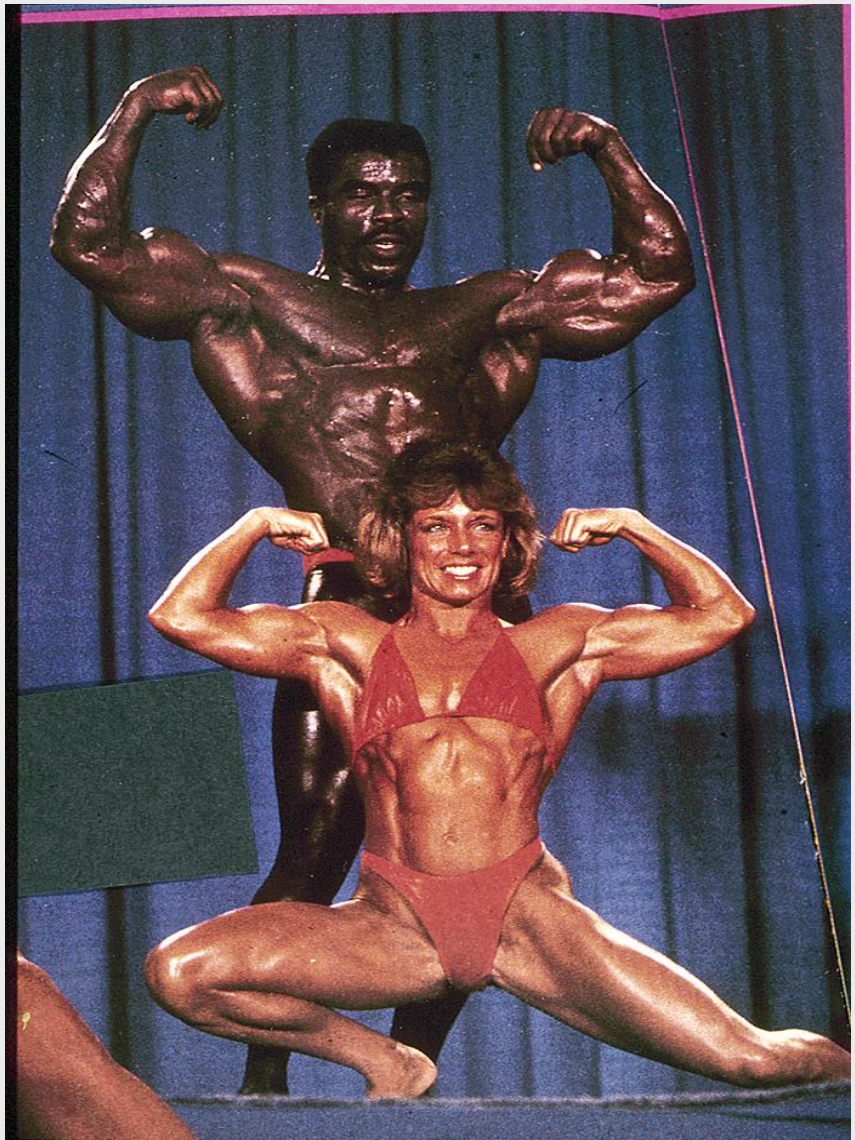
OTHER THERAPIES

- In spite of some optimistic case reports a controlled trial involving 39 patients of leukaphoresis and plasma exchange was no more effective than sham apheresis

Miller et al. N Eng J Med 1992; 326:1380

- Whole body irradiation, total lymphoid irradiation,thymectomy, extracorporeal photochemotherapy have never been subjected to adequate control trials.

WHAT TREATMENT FOR MYOSITIS HAS FAILED TO ACHIEVE!



ADDITIONAL CONSIDERATIONS – 1 -

- Use sunscreens

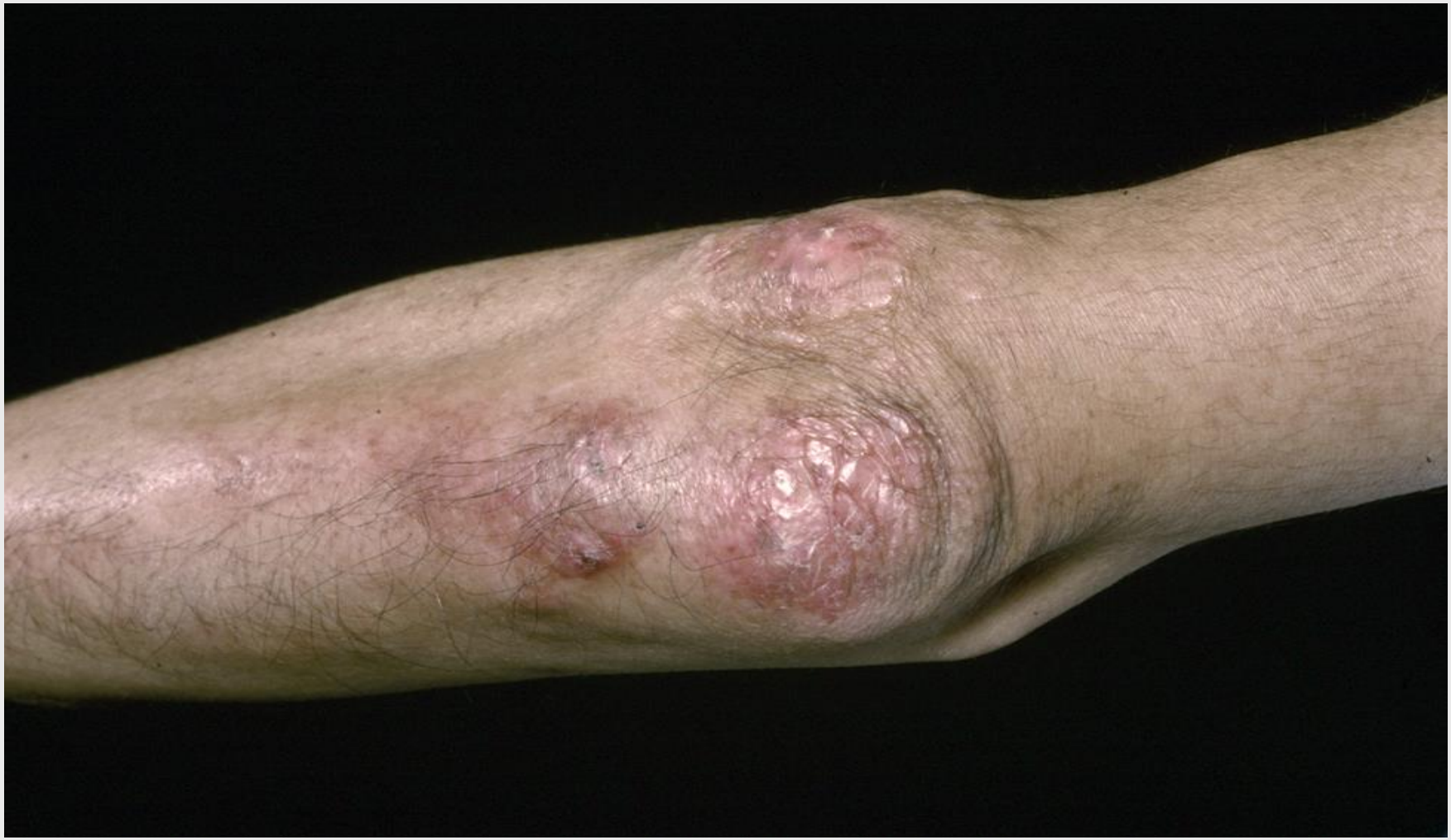
CUTANEOUS

- Consider topical steroids

- Hydroxychloroquine can improve the rash and lower steroid requirement
  - Woo et al. J Am Acad Derm 1984; 10: 582

- **BUT** no method of treating subcutaneous calcification is of proven benefit

ELBOW CALCINSOSIS



ADDITIONAL CONSIDERATIONS – 2 -

ARTICULAR

Co-existent polyarthralgia quite common

Usually steroid responsive

CARDIAC

Up to 70% of patients involved

Mostly asymptomatic

PULMONARY

Interstitial lung disease common

Response to immunosuppression variable

GASTRO-INTESTINAL

Dysphagia is up to 30%

Cricopharyngeal myotomy occasionally needed (Kagen et al. 1985)

ADDITIONAL CONSIDERATIONS – 3 -

Active exercise is discouraged during acute inflammation

Start passive range of motion exercises early to avoid joint contractures

Active exercise can be introduced when inflammation subsides (Hicks 1988),start with isometric exercises

Active resistive exercises can be considered in stable patients even if some disease activity persists (Escalante et al 1993).

PREDNISOLONE (0.5 – 0.75mg/kg)

Improvement

Prednisolone (0.5-0.75mg/kg)

↓prednisolone by 15-25%/month

Maintenance steroids likely to be required for 2 years

PREDNISOLONE (0.5 – 0.75mg/kg)

Improvement

↓prednisolone by 15-25%/month

Maintenance steroids likely to be required for 2 years

Poor response

Add

Azathioprine

2 mg/kg (less toxic)

or

Methotrexate

Up to 25 mg/wk

(higher response rate)

or both

Wait 4 - 6 months

If poor response… consider:

1. Is the diagnosis correct?
2. Other drugs neoral/cyclophosphamide/ Anti-TNF ∝
3. IvIg - can be used in severe cases much earlier

A FEW NOTES ON TREATMENT BEFORE 2006 – 1 -

- **Before corticosteroids and immunosuppressives the mortality rate was 50-70%**

  eg Medsger et al 1971

- **Even after their introduction the outlook was far from 'stellar' eg.**

  5yr survival – 52% **Benbassset et al 1985**

  8yr survival – 73% **Hochberg et al 1986**

A FEW NOTES ON TREATMENT BEFORE 2006 – 2 -

The common causes of death in ‘most’ series:-

- **Infection**
- **Lung disease**
- **Cardiac disease**
- **Malignancy**

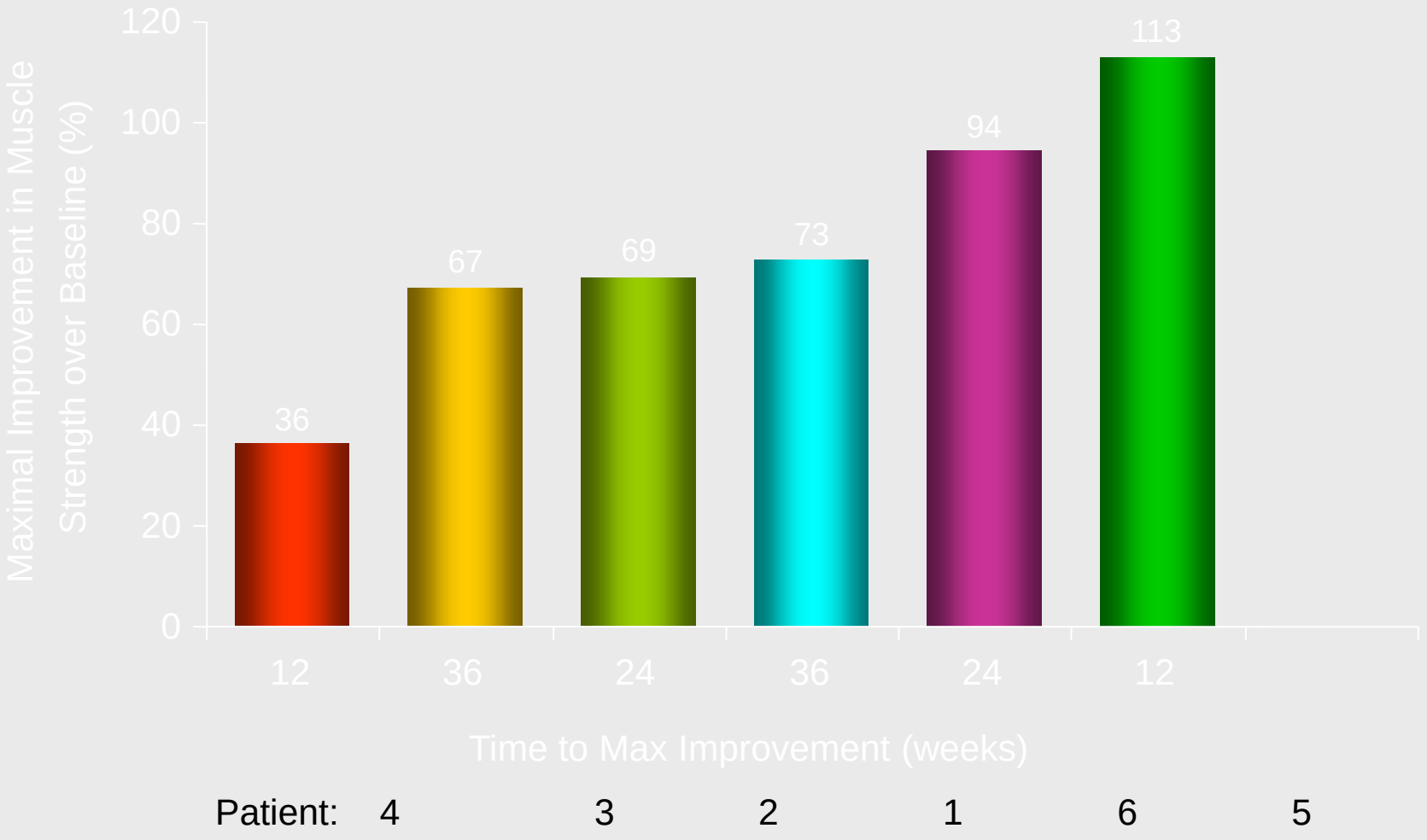
B-CELL TARGETED THERAPIES: DERMATOMYOSITIS

- All 6 achieved $CD20^+$ B-cell depletion
- Drug well tolerated
- Improvement noted in CK (baseline range 128–5600 U/L to 57–1168 U/L); FVC (maximum improvement range 33%–44%) and muscle strength

FVC, forced vital capacity.

Levine TD. *Arthritis Rheum*. 2005;52:601-607.

B-CELL TARGETED THERAPIES: DERMATOMYOSITIS



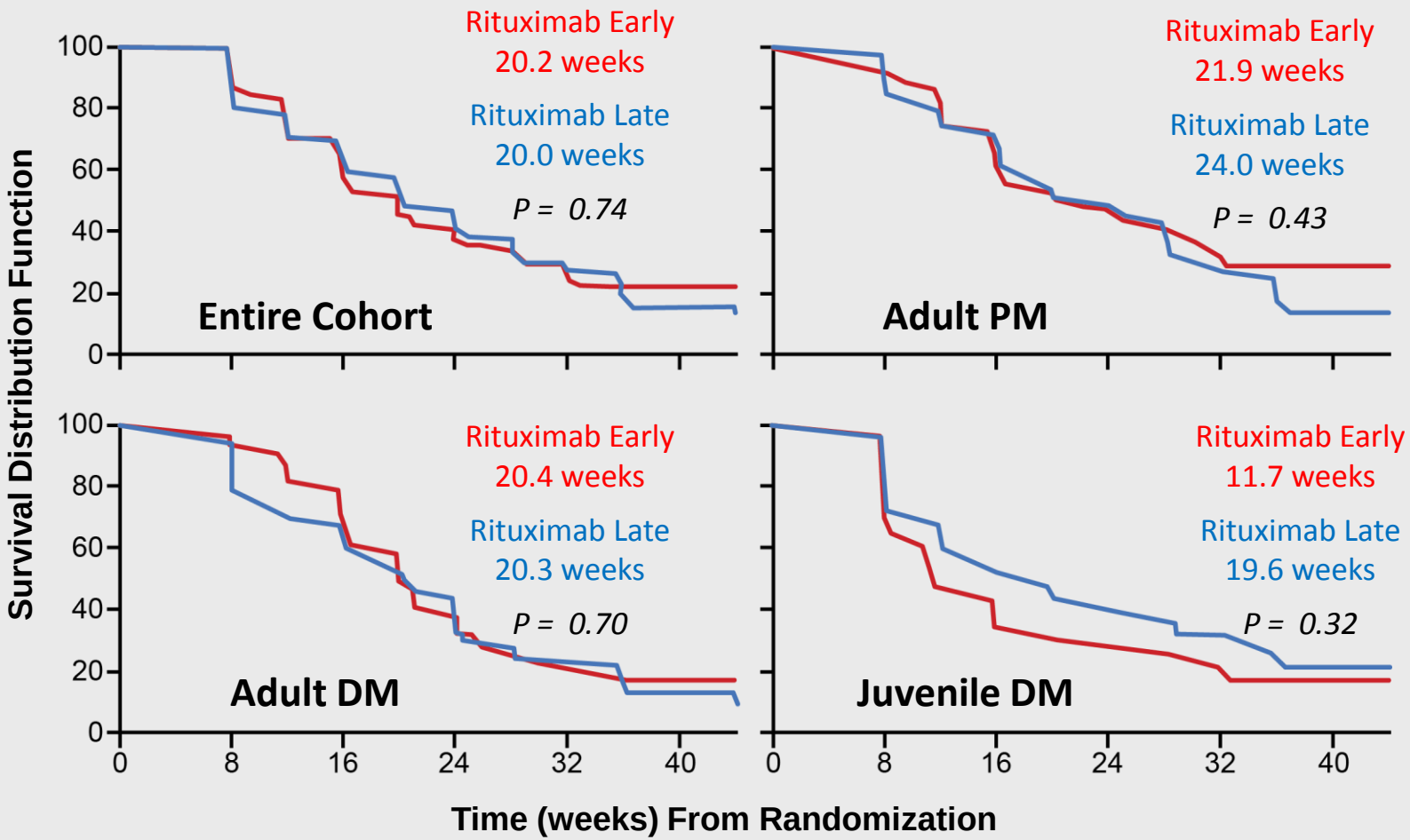
Levine TD. *Arthritis Rheum*. 2005;52:601-607.

BUT…

- The RIM (Rituximab in Myositis) trial involving >200 patients failed to show any benefit for Rituximab + SOC versus SOC + placebo.

- However the concomitant steroids and immunosuppressives were probably too high to make it likely that Rituximab could show benefit.

PRIMARY ENDPOINT IN RIM TRIAL: NO DIFFERENCE IN TIME TO RESPONSE [DOI]



In response criteria project, examined MD assessment of improvement at week 24

Oddis CV et al., Arthritis Rheum 2013;65(2):314-24.

THE USE OF RITUXIMAB IN THE TREATMENT OF IDIOPATHIC INFLAMMATORY MYOPATHY [IIM] -1-

Methods:

- **Bibliographic search of the PubMed database using the keywords**

Inflammatory myopathies **OR**

Anti-synthetase syndrome **OR**

Polymyositis **OR**

Dermatomyositis **OR**

AND

RITUXIMAB

(published up to July 2015)

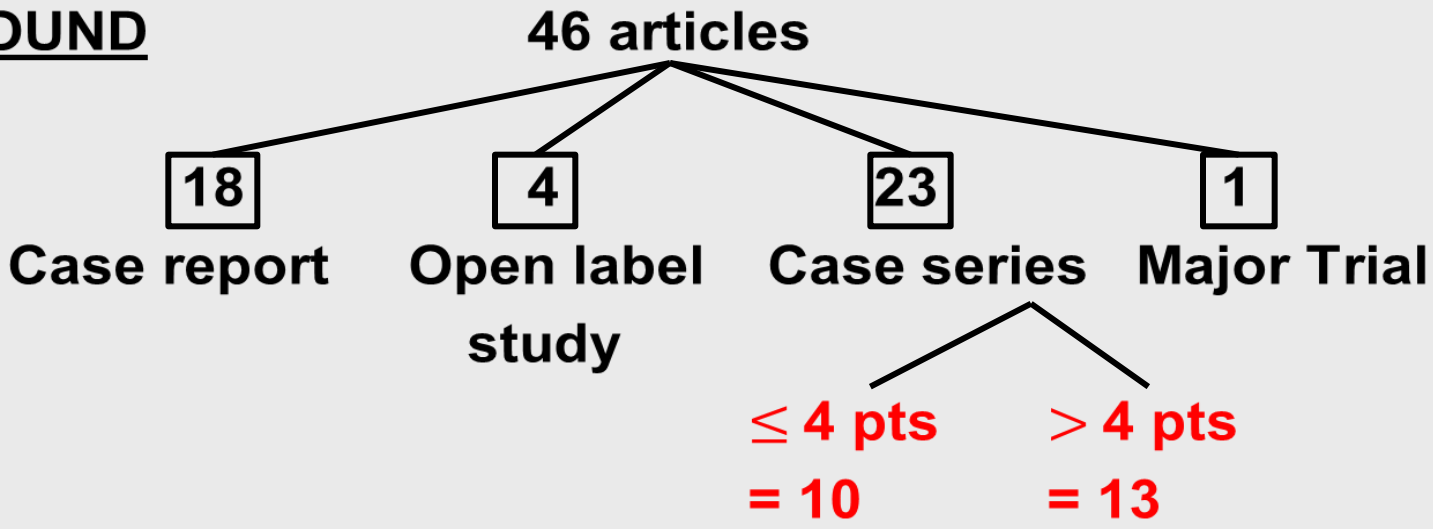
Fasano, Hajji, Loyo, Gordon, Isenberg. Submitted.

THE USE OF RITUXIMAB IN THE TREATMENT OF IDIOPATHIC INFLAMMATORY MYOPATHY [IIM] -2-

Methods:

We considered case reports and open label studies and clinical trials – 2 main regimes used 1g x 2 2/52 apart or 375/m^2 weekly x 4

WE FOUND



A CAUTIOUS OVERVIEW OF THE RESULTS!

- **447 patients treated [including 151 with DM; 142 with PM; 71 with JDM]**

muscle weakness	**– 410**	**(91.7%)**
alveolitis	**- 70**	**(15.6%)**
arthritis	**- 14**	**(3.1%)**

- **Overall 347 (77.6%) were reported to show some form of improvement.**

OTHER BIOLOGIC DRUGS THAT HAVE BEEN USED TO TREAT MYOSITIS

Abatacept

Infliximab

Adalimumab

Etanercept

Tocilizumab

Anakinra

Silfalimumab

(Fasano, Alves, Isenberg submitted)

ABATACEPT – BLOCKS APC/T-CELL

- **3 case reports [refractory PM; JDM; myositis overlap]**
- **each described some clinical benefit and ↓ enzyme level in ‘hard-to-treat’ cases**
- **ARTEMIS Trial (ongoing phase III)**

TNF α BLOCKADE

INFLIXIMAB	ADALIMUMAB	ETANERCEPT
Some encouraging early reports	1 case report of a hard-to-treat patient	Some encouraging early reports
2 small studies with n = 13 + n = 6 showed no benefit	↑ muscle strength ↓ CK	52 week pilot trial of 16 treatment naïve patients showed no benefits [apart from steroid sparing]
NOT recommended		(Ann Neurol 2011; 70; 427)

TOCILIZUMAB [IL-6R BLOCKER]

- **3 case reports [2PM, 1 overlap syndrome]**

- **In each of these hard-to-treat patients some clinical benefit and improved enzyme levels**

ANAKINRA – ANTI-IL-1

- **A 12 month open-label trial reported an improvement in 7/15 patients with refractory myositis** (Zong et al. Ann Rheum 2014; 75; 913)

- **nb the inflammatory infiltrates were still present in repeat biopsies and the IL-1 expression was not correlated to clinical responses**

SILFALIMUMAB – ANTI-IFN α

- **Phase 1b trial – a moderate suppression of genes induced by type 1 IFN (which is highly overexpressed in myositis patients compared to controls)**

- **Some improvement in muscle strength (correlated with gene neutralization) was noted (Higgs et al. Ann Rheum Dis 2014; 73; 256)**

INVESTIGATOR LED STUDY

OPTIONS FOR A RITUXIMAB STUDY

- Treat at the time of the diagnosis
- Treat those who have failed steroids and 2 immunosuppressives

PROS AND CONS

At Diagnosis

Pros

- Original
- Not confounded by previous/current immunosuppression

Cons

- Harder to recruit
- Harder to fund

Post-Conventional Therapy

Pros

- Easier to recruit
- (Probably) easier to fund

Cons

- Not original
- Greater patient diversity [duration/damage/ prior variable activity/ therapy]

AT DIAGNOSIS – TRIAL - THOUGHTS

- **Could be:-**

- **In newly diagnosed, biopsy-confirmed, patients with IIM**

Rituximab at time 0 and 6mns followed by Azathioprine, MTX or MMF	**vs**	**Steroids and Azathioprine, MTX or MMF**

Primary endpoint at one year.

POST-CONVENTIONAL THERAPY

- Could be:-

- **In patients with established disease who have failed/done inadequately with steroids and 2 immunosuppressives eg MTX/Azathioprine**

Rituximab + S.O.C.
[viz Prednisolone
(max 20mgm/dy)
+ MMF]
2 + 3g/dy

vs.

S.O.C.

END POINTS – 1 YEAR END POINT

Possibilities

- **Use the agreed IMACS/PRINTO myositis response criteria [quite demanding].**

OR

- **Agree on minimal data set viz muscle strength/CPK/patient and physician VAS.**

OR

- **Use the loss of MITAX As and Bs (complete or partial) as the end point.**

QUESTIONS FOR DISCUSSION

- **IMACS/PRINTO end points [quite demanding]**

OR

- **Agree on minimal data**
  - **muscle strength**
  - **CPK**
  - **patient and physician VAS**
  - **some centres using the full MITAX end points**

- **Enrolment at diagnosis OR refractory disease?**

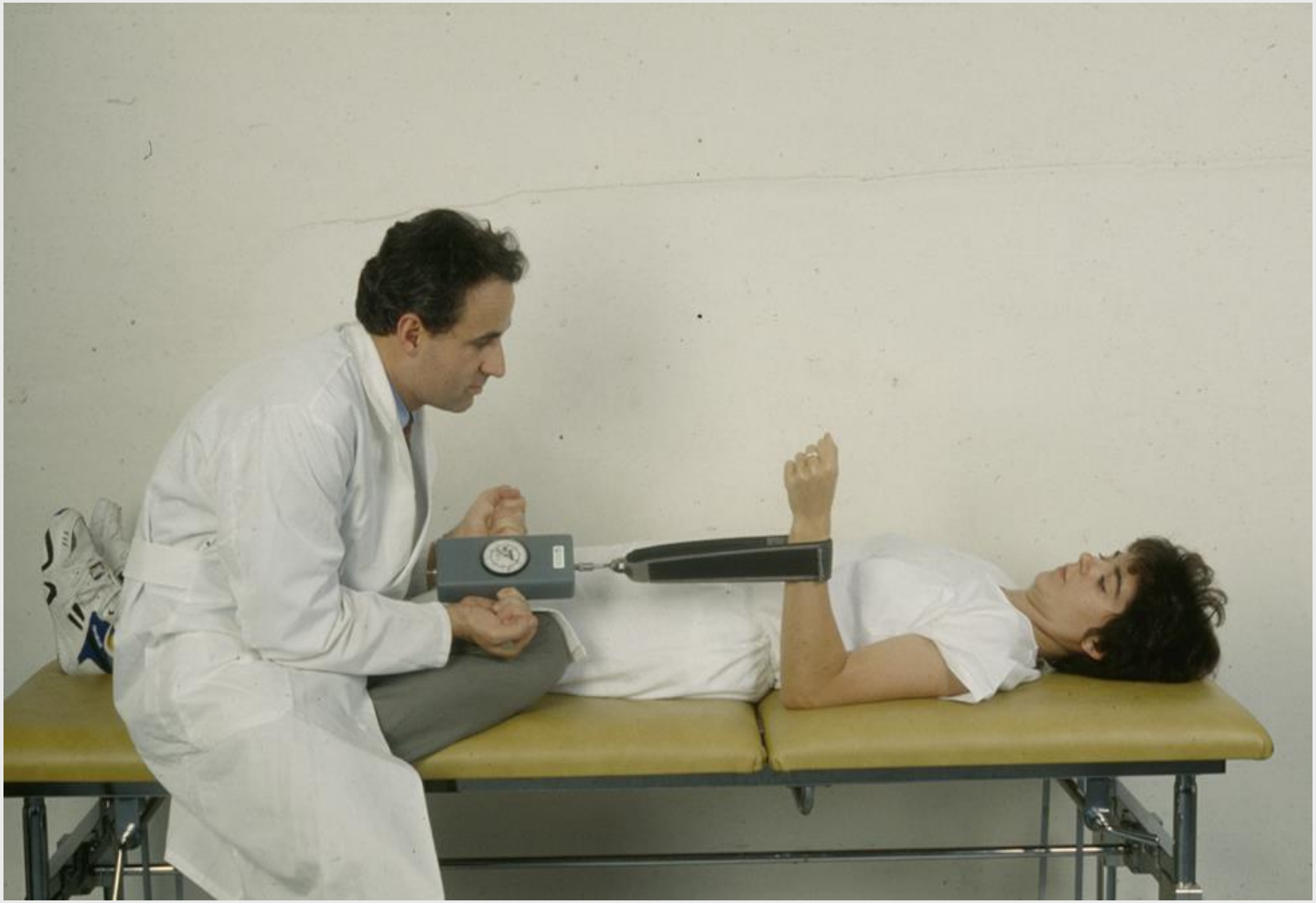
Final consensus definition of improvement (Reserve Slide)

- Uses absolute % change in core set measures (CSMs)
- Conjoint analysis (1000minds) provides different weights to the various CSMs
  - MMT/CMAS > MD Global Activity > Extramuscular Global/DAS > Patient VAS > HAQ/CHAQ > Muscle enzymes/CHQ-PhS
- Uses same definition for adult DM/PM and juvenile DM
  - Different optimal cut points for each
- Defines criteria for minimal, moderate and major improvement
  - Major improvement is provisional for adult DM/PM
- Total improvement score is associated with magnitude of improvement
- Selected as a primary endpoint for future clinical trials
  - Pending approval from ACR/EULAR as final response criteria

Devere & Bradley - Polymyositis: its presentation and mortality
Brain 1975; 98: 637-66

- 118 patients studied
- proximal lower limb weakness = 92%
- proximal upper limb weakness = 86%
- EMG studies performed in 98 - normal in 11
- open muscle biopsies in 103 - normal in 11

MANUAL MYOMETER DEMONSTRATED



FACTORS AFFECTING CREATININE KINASE LEVELS – OTHER CAUSES OF ELEVATED LEVELS – 1 -

- ethnicity
- recurrent strenuous exercise
- drugs
- endocrine/metabolic disorders
- other conditions
- other muscle diseases
- dystrophy
- rhabdomyolysis
- myocardial infarction
- metabolic

FACTORS AFFECTING CREATINE KINASE LEVELS – CAUSES OF LOW CK LEVELS IN ACTIVE MYOSITIS – 2 -

- **Circulating inhibitor**
- **Steroid treatment without disease suppression**
- **Advanced disease with atrophy i.e. damage not activity**
- **?? concurrent autoimmune rheumatic disease**
- **unexplained!**

	Lupus + Myositis n = 11	Primary Myositis n = 19
F:M	10:1	12:7
PM:DM	7:4	12:7
Age at onset	33 yrs (21-47)	36 (29-66)
Initial CK	11.2* (1.3-50)	10.7* (0.8-28)
Initial quads strength	49% of normal	52% of normal

*expressed as a multiple of the upper limit of normal.

Garton & Isenberg. BJR 1997; 36: 1067

MUSCLE BIOPSY - PROBLEMS

- Open vs needle vs conchotome
- Focal nature of the lesion in some cases
- Must look out for:

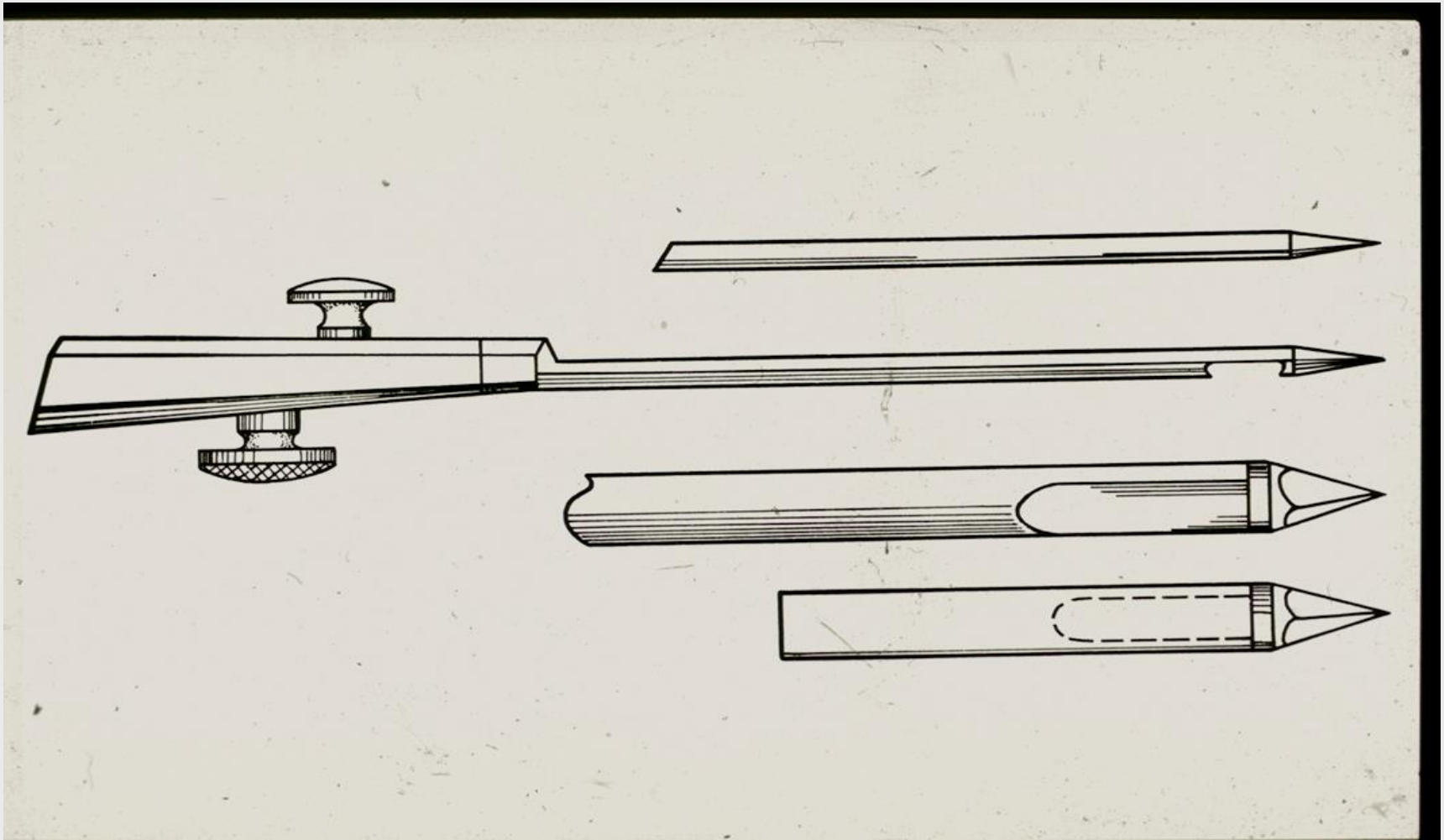
- fibre hypertrophy = dystrophy

- inclusion bodies = IBM

- widespread necrosis with profuse regeneration = rhabdomyolysis

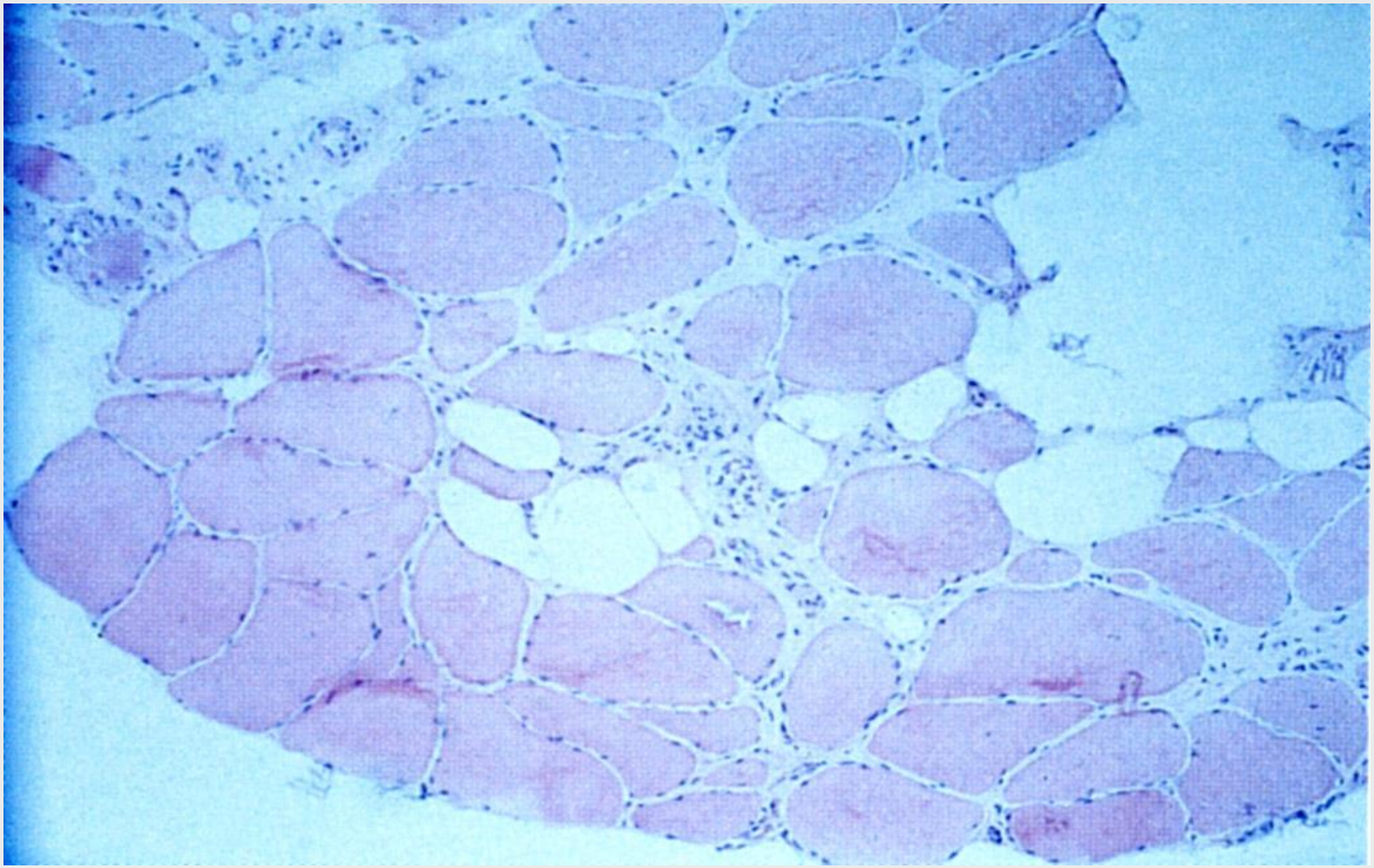
(+ myoglobinuria)

DUCHENNE'S MUSCLE BIOPSY NEEDLE

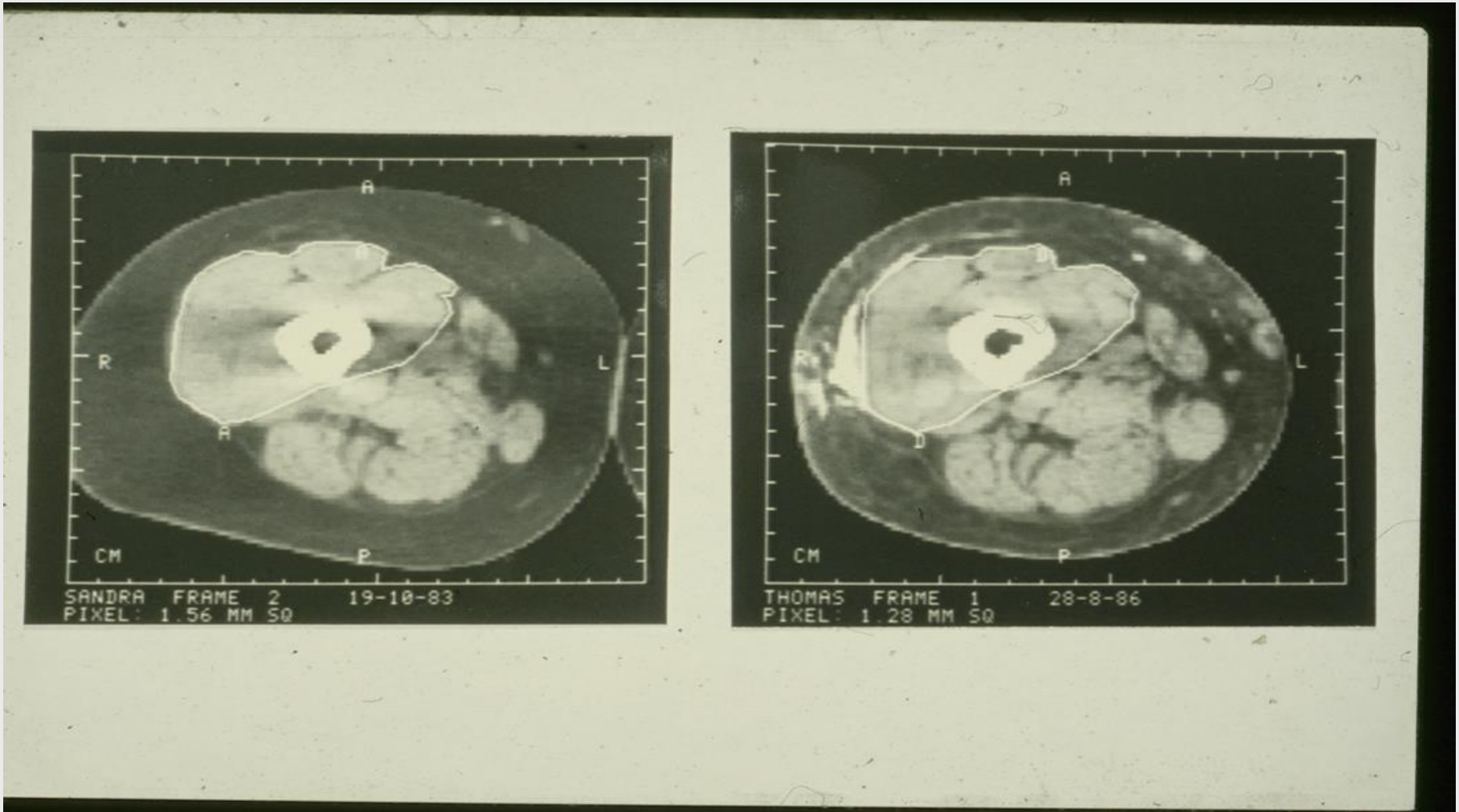


MODERN MUSCLE BIOPSY NEEDLE

INCLUSION BODY MYOSITIS



CT SCAN QUADRICEPS – 3-YEAR FOLLOW-UP



MRI SCAN - SOLEUS