MAYO CLINIC

Discovery, Understanding, and Progress in Myositis

Steven Ytterberg, M.D.

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Disclosures

Financial:

- Dynavax Corp.
- Pfizer
- Mallinckrodt
- American Board of Internal Medicine

Off label use:

- Everything other than steroids and ACTH

What has changed in the last 40 years and what can we look forward to seeing as a result of current research?

Changes Over 40 years

- Diagnosis, defining disease, criteria
- Evaluation
- Understanding pathogenesis
- Treatment

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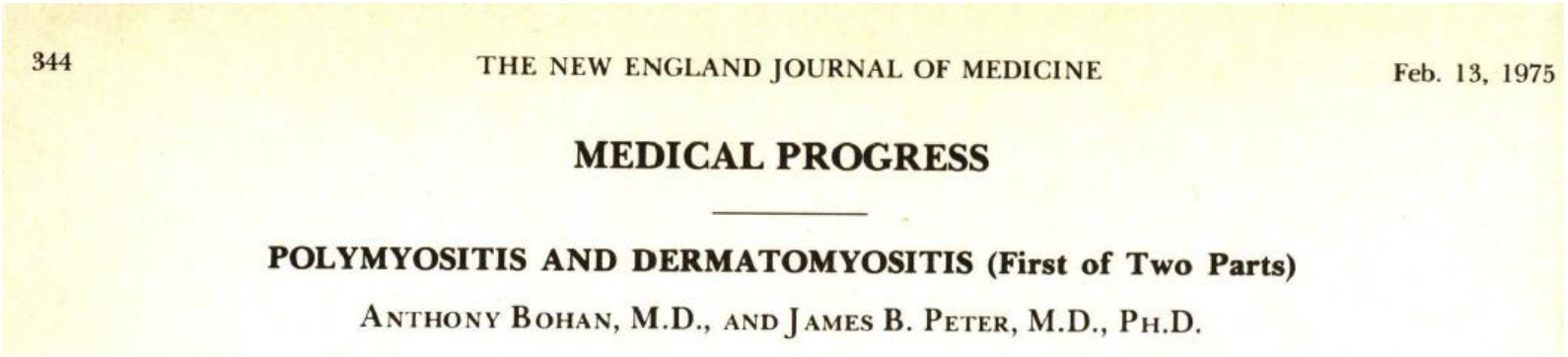
Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)

- Isolated, adult
- Juvenile
- Malignancy
- Overlap



344 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 13, 1975

MEDICAL PROGRESS

POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)

ANTHONY BOHAN, M.D., AND JAMES B. PETER, M.D., PH.D.

Bohan & Peter, N Engl J Med 292: 344, 405, 1975
Bohan et al., Medicine 56: 255, 1977

PM/DM Classification Criteria

- Proximal muscle weakness
- Elevated serum levels of skeletal muscle enzymes
- Myopathic changes on EMG
- Muscle biopsy evidence of inflammation
- Skin rash

Definite PM or DM: 4 criteria

Probable PM or DM: 3 criteria

Possible PM or DM: 2 criteria

Bohan & Peter, N Engl J Med 292: 344, 405, 1975
Bohan et al., Medicine 56: 255, 1977

Problems with the Bohan & Peter criteria

- Inclusion body myositis (IBM) can be classified as PM
- Newer autoimmune muscle disorders, e.g., immune-mediated necrotizing myopathy, can be classified as PM
- Doesn’t account for amyopathic DM

Others

- Tanimoto

  Tanimoto et al., J Rheumatol 1995; 22: 668-74

- Targoff

  Targoff et al., Curr Opin Rheumatol 1997; 9: 527-35

- Dalakas & Hohlfeld

  Dalakas & Hohlfeld, Lancet 2003; 362: 971-82

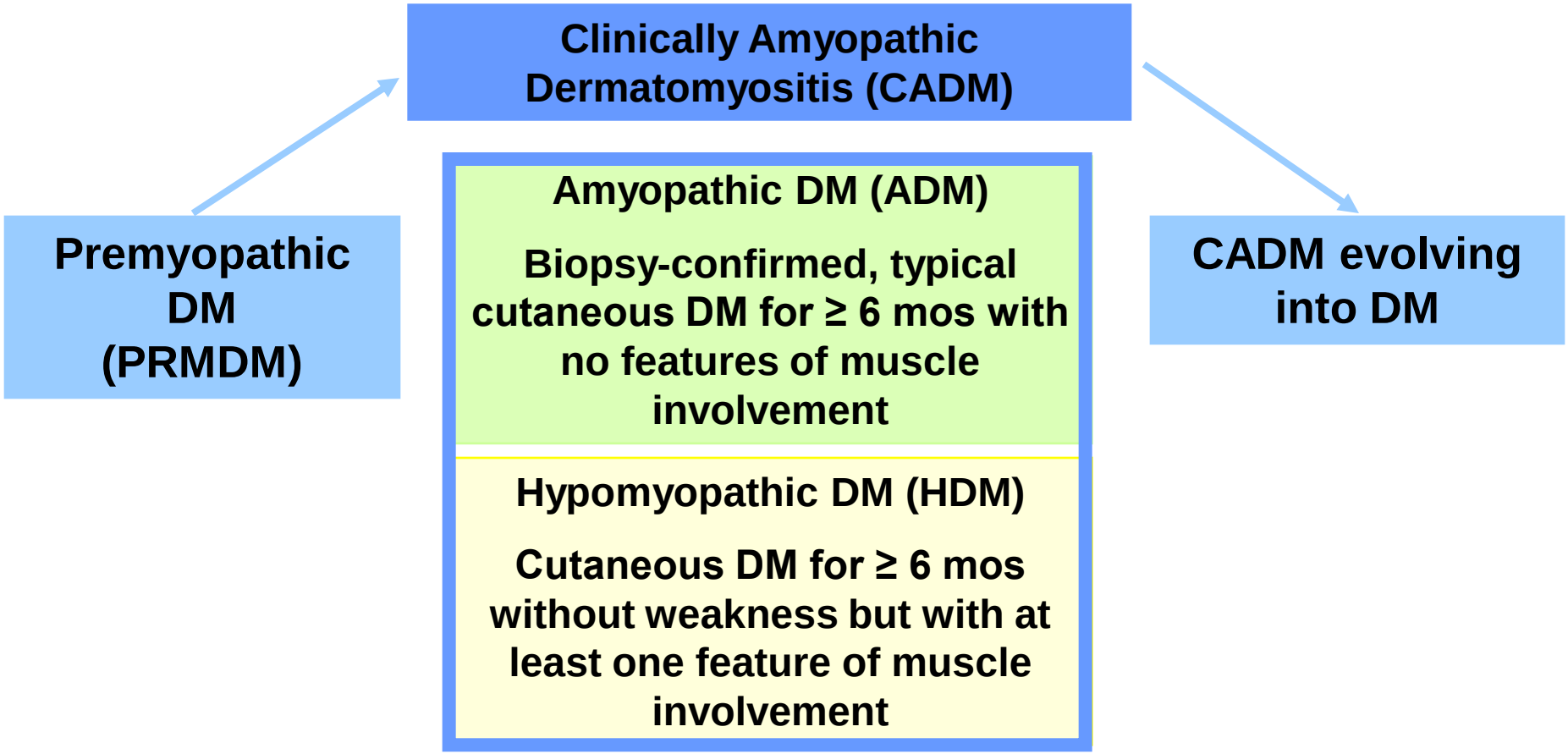
- European Neuromuscular Centre

  Hoogendijk et al., Neuromsucul Disorder 2004; 14: 337-45

- International Myositis Classification Criteria Project

  Lundberg et al., J Intern Med 2016; 280: 39-51

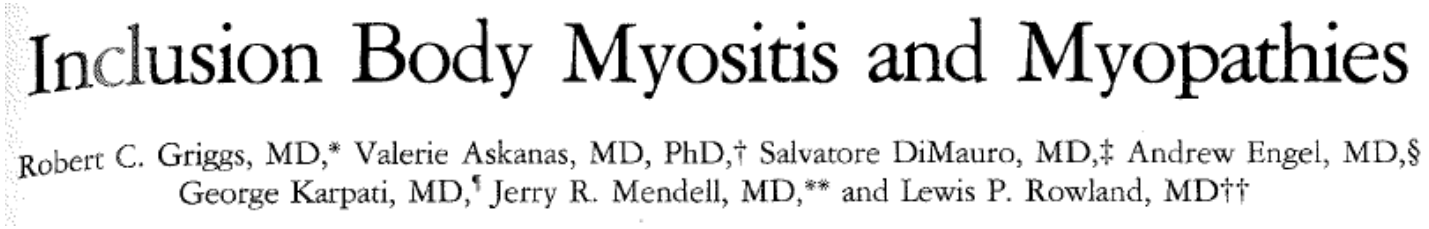
Amyopathic Dermatomyositis (Dermatomyositis siné myositis)



Gerami et al., J Am Acad Dermatol 54:597-613, 2006

Inclusion Body Myositis

- First description
  - *Chou, Science 1967; 158: 1453-5*
- Term “inclusion body myositis”
  - *Yunis & Samaha, Lab Invest 1971; 25: 240-8*
- Comprehensive review and proposed criteria
  - *Griggs et al., Ann Neurol 1995; 38: 705-13*



Inclusion Body Myositis and Myopathies

Robert C. Griggs, MD,* Valerie Askanas, MD, PhD,† Salvatore DiMauro, MD,‡ Andrew Engel, MD,§
George Karpati, MD,¶ Jerry R. Mendell, MD,** and Lewis P. Rowland, MD††

Anti-synthetase Syndrome

- Anti-aminoacyl-tRNA synthetase antibodies
- PM/DM
- Interstitial lung disease
- Inflammatory arthritis
- Raynaud's phenomenon
- Mechanic's hands
- Fever

Antisynthetase Antibodies

		Frequency (%)		
Antigen	**tRNA synthetase**	**JDM***	**ADM***	**Non-white**
Any		1-5	30	AA 29
Jo1	Histidyl-	2-5	25-30	AA13
PL12	Alanyl-	1-3	<5	
PL7	Threonyl-	<1	<5	Japanese 17
EJ	Glycyl-	<1	<5	
OJ	Isoleucyl-	<1	<5	
KS	Asparagynyl-	NA	<1	
HA	Tyrosyl-	NA	<1	
ZA	Phenylalanyl-	NA	<1	

*Caucasian

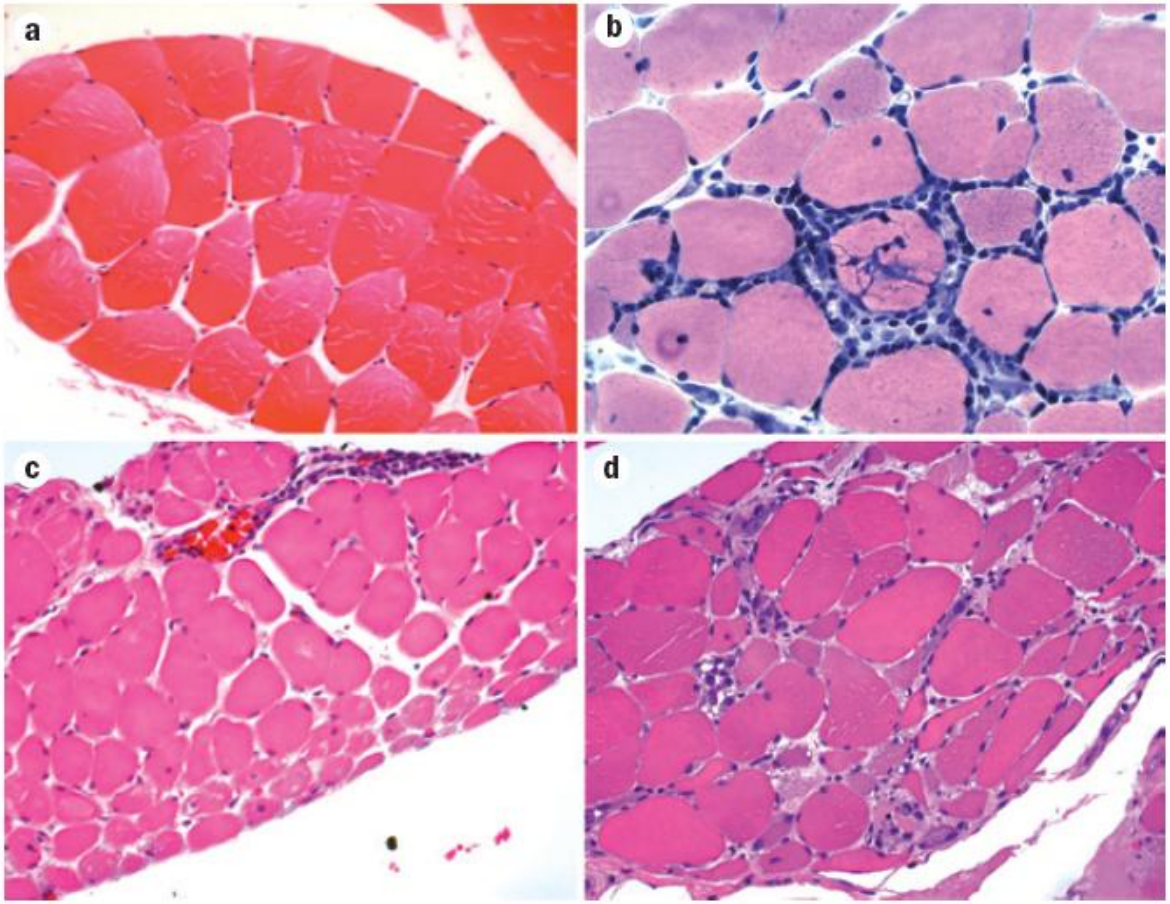
Robinson & Reed, Nat Rev Rheumatol 2011; 7: 664-75

Immune-mediated Necrotizing Myopathy

- Characterized by muscle biopsy with necrotic muscle fibers without inflammation
- Specific autoantibodies
  - Anti-SRP
  - Anti-HMGCR
    - Often associated with statin use

Christopher-Stine, et al. Arthritis Rheum 2010; 62: 2757-66
Mammen, et al. Arthritis Rheum 2011; 63: 713-21

Muscle histopathology



a) Normal muscle
b) PM – endomysial inflammation
c) DM – perifascicular atrophy
d) Necrotizing myopathy

Mammen, Nat Rev Neurol 2011; 7:343-54

Changes Over 40 years

- Diagnosis, defining disease, criteria
- Evaluation
- Understanding pathogenesis
- Treatment

Evaluation of Myositis – 1976

- Muscle weakness
- Elevation of muscle enzymes
- Electromyogram (EMG) changes
- Muscle biopsy

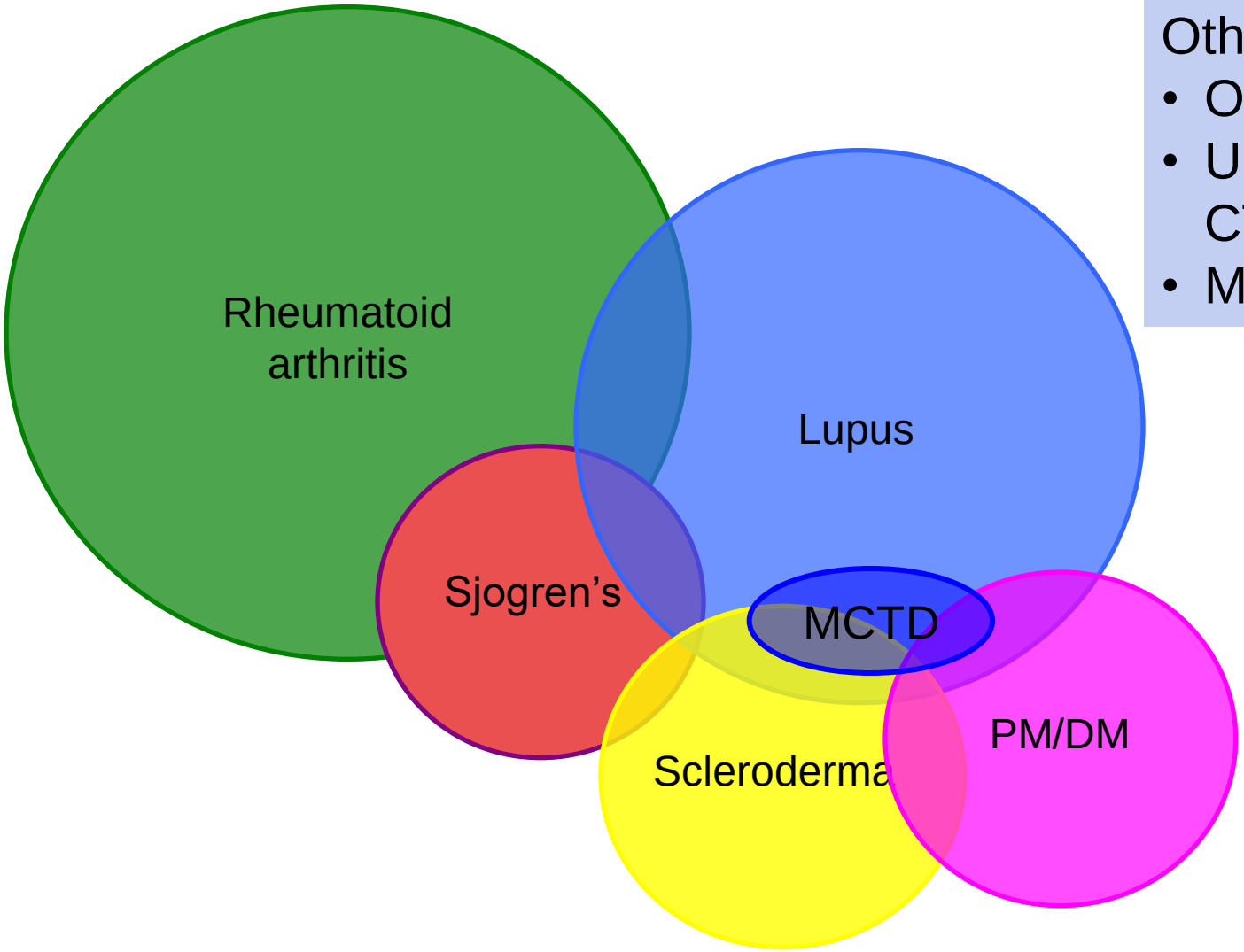
Evaluation of Myositis – 2016

- Muscle weakness – validation of testing
- Elevation of muscle enzymes – isotypes
- Electromyogram (EMG) changes
- Muscle biopsy – recognition of IBM and necrotizing myopathy
- MRI of muscle
- MR spectroscopy of muscle
- Muscle elastography?

Evaluation of Myositis – 2016

- Recognition that these are systemic disorders and not just muscle problems
  - Interstitial lung disease
  - Association with other autoimmune disorders

Autoimmune Connective Tissue Diseases



Other terms:

- Overlap CTD
- Undifferentiated CTD
- Mixed CTD

Core Set Measures to Assess IIM

International Myositis Outcome Assessment Collaborative Study Group (IMACS)

- Manual muscle strength testing
- Functional assessment - HAQ or CHAQ
- Global assessment
  - Physician
  - Patient/parent
- Assessment of extra-muscular activity - MDAAT/MITAX or CMAS
- Muscle enzymes - CK, aldolase, AST, ALT, LDH

Rider et al., Arthritis Rheum, 2004; 50: 2281-90

IMACS Preliminary Definitions of Improvement

- 3 of any 6 core set measures improved by ≥ 20%

- With no more than 2 worse by ≥ 25% (which cannot include MMT)

Rider et al., Arthritis Rheum, 2004; 50: 2281-90

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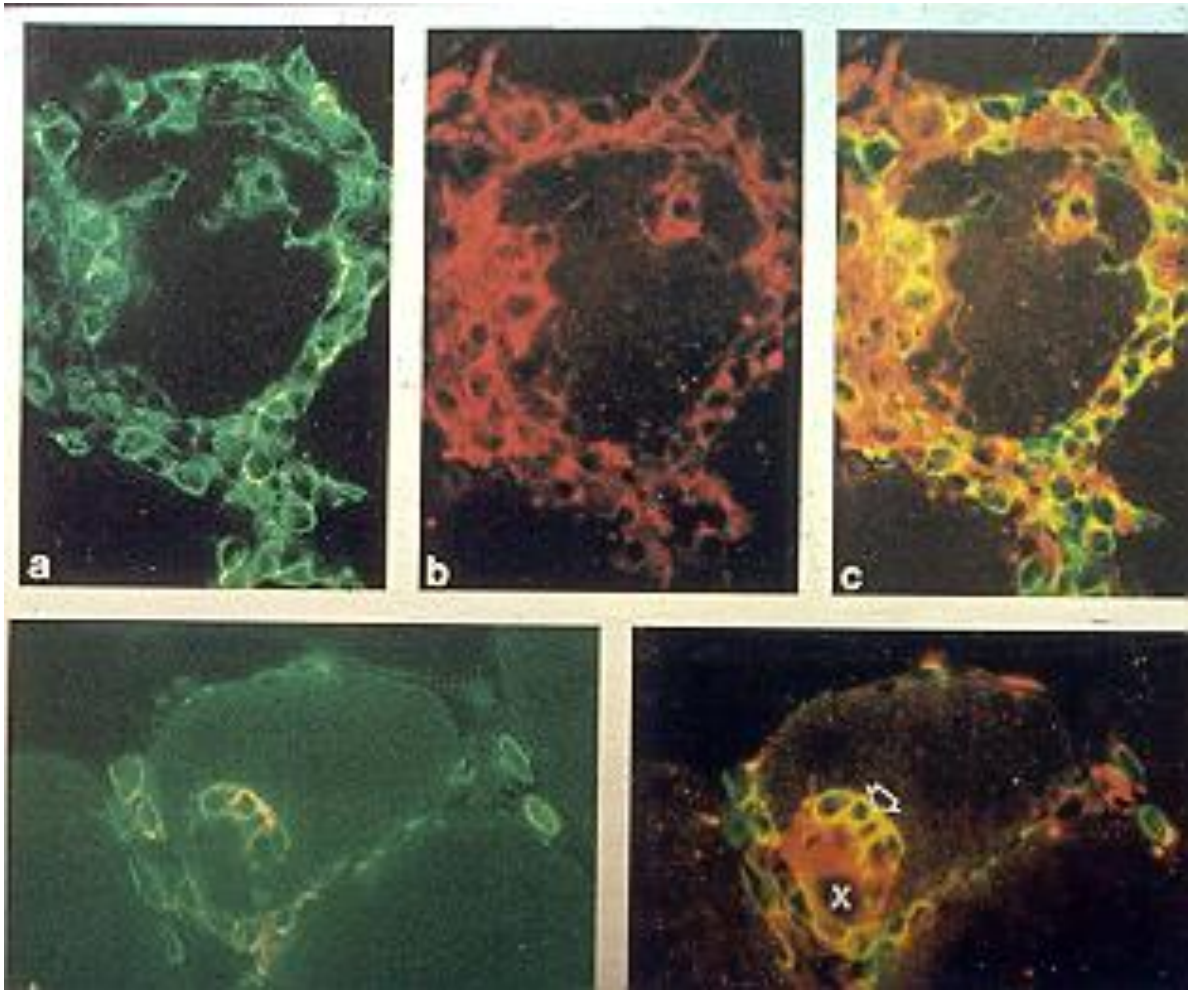
Cytotoxic T-cells Damage Muscle PM/IBM



Arahata & Engel, Ann Neurol 16:193, 1984

Humoral Immune Mechanisms in DM/JDM

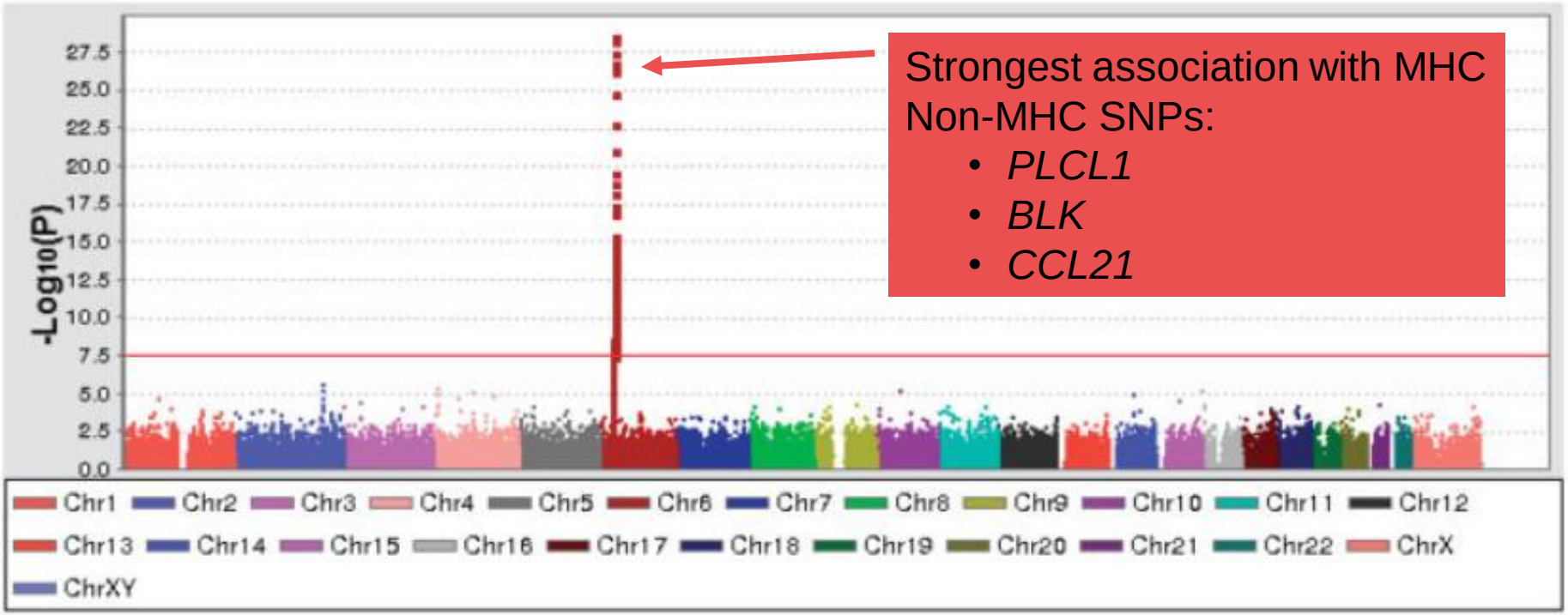
- Vasculopathy
- Deposition of complement components in vessels
- Th17 helper cells

Type I Interferon in DM Pathogenesis

- Type I interferon (IFN) activated in patients with DM, as is seen in systemic lupus erythematosus (SLE)
- Type I IFN is a signal generated when the body senses viral infection, among other things
- Type I IFN protects uninfected cells from becoming infected

DM is not PM with a rash

Genetics Factors in DM/JDM



Strongest association with MHC

Non-MHC SNPs:

- *PLCL1*
- *BLK*
- *CCL21*

Miller et al., Arthritis Rheum 2013; 65: 3239-47

Autoantibodies are frequent in IIM

Antibodies

- Immunoglobulin
- Produced by plasma cells in the immune system
- Identify and neutralize viruses and bacteria
- Each recognizes a unique protein (antigen)

Autoantibodies

- Antibodies directed toward an individual's normal proteins
- Autoantibodies may:
  - Cause disease
  - Simply be markers of disease

Some examples

Autoantibody	Target	Disorder
Antinuclear antibodies (ANA)	Contents of cell nuclei	Lupus and related conditions
Rheumatoid factor (RF)	IgG	Rheumatoid arthritis
Anti-Jo-1	Histidyl tRNA synthetase	Polymyositis with ILD
Anti-PR-3 (c-ANCA)	Neutrophil proteinase-3	Granulomatosis with polyangiitis
Anti-thyroid antibodies	TPO Thyroglobulin	Hashimoto's thyroiditis
Anti-AChR	Acetylcholine receptor on muscle	Myasthenia gravis
Anti-TTG	Tissue transglutaminase	Celiac disease

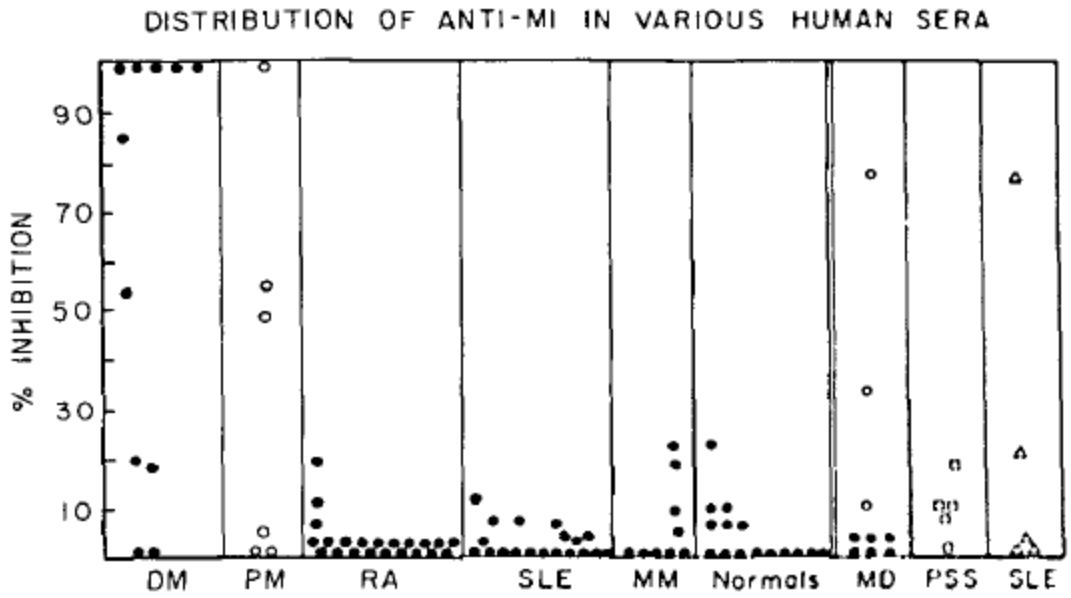
CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY 5, 12–20 (1976)

Description of a Serological Reaction Characteristic of Polymyositis[1]

MORRIS REICHLIN AND MARTHA MATTIOLI

Departments of Medicine and Biochemistry, SUNY at Buffalo School of Medicine, Veterans Administration Hospital, Buffalo, New York 14215

Received May 1, 1975



Reichlin & Mattioli, Clin Immunol Immunopathol 1976; 5: 12-

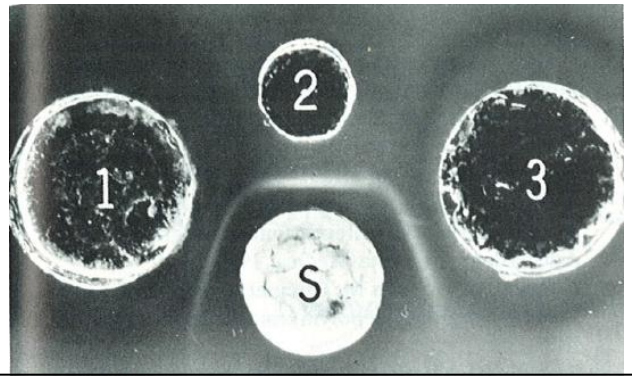
ARTHRITIS
&
RHEUMATISM

OFFICIAL JOURNAL OF THE AMERICAN RHEUMATISM ASSOCIATION
SECTION OF THE ARTHRITIS FOUNDATION

HETEROGENEITY OF PRECIPITATING ANTIBODIES IN POLYMYOSITIS AND DERMATOMYOSITIS

Characterization of the Jo-1 Antibody System

MASAHIKO NISHIKAI and MORRIS REICHLIN



1	Human muscle extract, partially purified
2	Column-purified CTE
3	Crude calf liver extract
S	Jo-1 monospecific antibody

Table 5. Incidence of Jo-1 antibody

	No. of patients	No. positive	% positive
Polymyositis	26	8	30.8
Dermatomyositis	22	1	4.5
Overlap syndromes*			4.5
PM–PSS	11	1	
PM–SLE	4	0	
PM–RA	2	0	
PM–Sjögren's	5	0	
Systemic lupus erythematosus	22	0	0
Progressive systemic sclerosis	11	0	0
Rheumatoid arthritis	9	0	0
Myasthenia gravis	14	0	0
Progressive muscular dystrophy	12	0	0
Normal subjects	12	0	0

* PM = polymyositis; PSS = progressive systemic sclerosis; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis. Total patients with overlap syndromes was 22.

Nishikai & Reichlin, Arthritis Rheum 1980; 23: 881-8

Non-specific Autoantibodies in Myositis

Percent of Patients with Various Autoantibodies

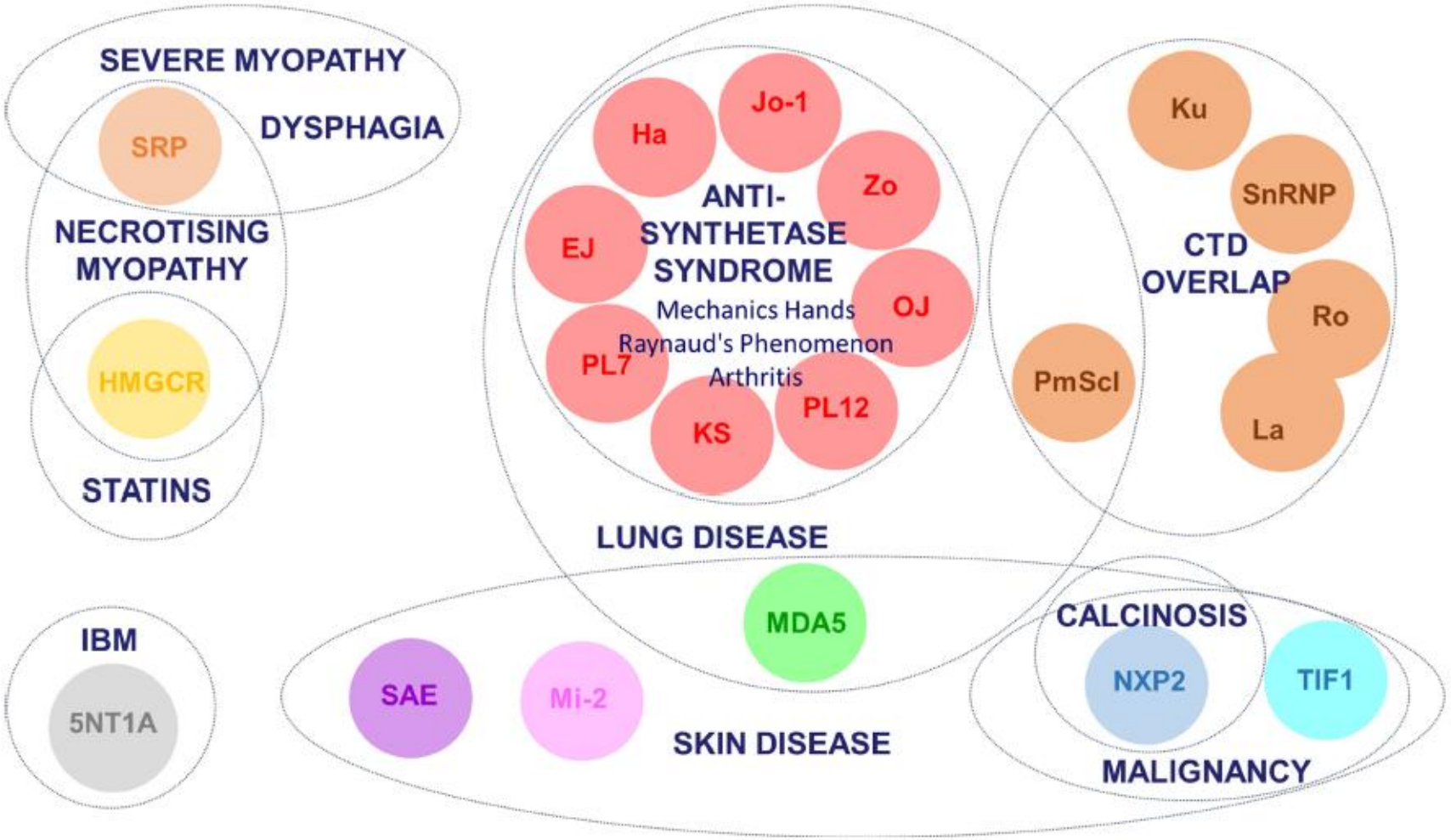
Antibody	All (n=212)	PM (n=58)	DM (n=79)	CTM (n=36)	CAM (n=13)	IBM (n=26)
ANA	52	40	62	77	31	23
ds-DNA	5	3	3	11	8	4
SSA/Ro	12	12	11	17	0	12
SSB/La	8	5	6	19	8	8
Sm	3	0	1	17	0	0
U1RNP	11	7	13	25	0	0
PM/Scl	2	0	4	3	0	0
RF	6	5	8	8	0	4

Love et al, Medicine 1991; 70: 360-74

Serologic Subgroups of IIM: Myositis-Specific Antibodies (MSA)

Feature	Synthetase	SRP	Mi-2
Clinical	Arthritis, ILD fever, Raynaud's	Cardiac myalgias; black women	Classic DM
Rate	Acute	Very acute	Acute
Severity	Severe	Very severe	Mild
Season	Spring	Fall	Unknown
Response	Moderate	Poor	Good
Prognosis	Poor (70%)	Terrible (25%)	Good (~100%)
Frequency	20-25%	<5%	5-10%

Myositis Specific Autoantibodies



Betteridge & McHugh, J Intern Med 2015; Epub

Why do MSA matter?

- Understand the cause of disease and/or mechanisms leading to specific clinical features
- Prognosis – may predict:
  - Need for more or less treatment
  - Need for more or less evaluation
- If they cause disease they might be a target for treatment

Changes Over 40 years

- Diagnosis, defining disease, criteria
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Treatment

1976

- Prednisone
- Prednisone
- Prednisone
- ? immunosuppressives

2016

- Prednisone
- Immunosuppressives
- IVIg
- Biologic agents

The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 141, No. 18 — CHICAGO, ILLINOIS — DECEMBER 31, 1949

EFFECTS OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) THERAPY

J. R. ELKINTON, M.D.
A. D. HUNT Jr., M.D.
L. GODFREY, M.D.
W. W. McCRORY, M.D.
A. G. ROGERSON, M.D.
and
J. STOKES Jr., M.D.
Philadelphia

The discovery by Hench and co-workers [1] of the dramatic improvement in rheumatoid arthritis induced by the administration of certain steroids of the adrenal cortex and adrenocorticotropic hormone (ACTH) of the pituitary, has provided a clue to the pathogenesis of a wide variety of related diseases. These workers clearly established that 17-hydroxy-11-dehydrocorticosterone (Kendall's compound E, or cortisone), 17 hydroxycorticosterone (compound F) and pituitary adrenocorticotropic hormone produced immediate remissions in the disease, remissions which lasted as long as these substances were administered. Improvement was also obtained in patients with acute rheumatic fever.[2] Since this report appeared other investigators have confirmed these observations and widened the scope of disease states in which adrenocortical hormones are efficacious. Thorn and co-workers [3] have reported the successful use of pituitary adrenocorticotropic hormone in 9 patients with rheumatoid arthritis, 3 with rheumatic fever, 3 patients with disseminated lupus erythematosus and 1 with gout. Rheumatoid arthritis has also been reported to have responded with good results to cortisone by Boland and Headley [4] and to pituitary adrenocorticotropic hormone by Markson.[5]

These spectacular though transitory therapeutic successes have captivated medical and lay minds alike. Unfortunately, the wide publicity given to the subject has left the impression, at least with the laymen, that the suffering arthritic patient has but to await the volume production of these substances for a complete resolution of his problems. That such is not the case was indicated by the evidence presented at the recent conference of investigators of the problem, sponsored by Armour and Company in Chicago.[6] Two facts were apparent: (1) that the fundamental process by which adrenal cortical steroids affect these diseases is unknown and unmeasured in terms of the known metabolic functions of the adrenal cortex, and (2) that, although the use of pituitary adrenocorticotropic hormone and cortisone in human patients may result in dramatic remissions of these diseases, such use may also be attended with serious complications. The clinical and metabolic studies reported in this paper are a part of this evidence.

CLINICAL MATERIAL AND METHODS OF STUDY

Pituitary adrenocorticotropic hormone [7] was administered to 8 patients with the following diseases: juvenile rheumatoid arthritis (2), disseminated lupus erythematosus (2), dermatomyositis (1), acute rheumatic fever (2) and status asthmaticus (1). The duration of therapy and dosage of the compound varied considerably according to the supply of the adrenocortical hormone and to the clinical response of the patient. Treatment was discontinued in 4 patients because of failure to respond or because the supply of the drug was temporarily exhausted. The other 4 patients were treated for prolonged periods as long as one hundred and forty-nine days.

Metabolic studies were conducted for shorter periods at the beginning of administration and later in the course

Elkington et al., JAMA, 1949; 141: 1273-9

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3. Four patients were treated for prolonged periods. One patient with lupus and one with dermatomyositis, both apparently moribund before therapy, have maintained remission of symptoms after cessation of treatment with the drug. One patient with disseminated lupus or generalized collagen disease became refractory to the drug and died. One patient with acute rheumatoid arthritis tended to obtain lessening degrees of relief from increasing doses of the adrenocortical preparation, which had to be withdrawn because of the appearance of signs of Cushing's syndrome.

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CORTICOTROPHIN AND CORTISONE THERAPY IN DERMATOMYOSITIS

BY

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Consultant Physician, Portiuncula Hospital, Ballinasloe, Co. Galway

Summary

Three cases of dermatomyositis treated by corticotrophin and cortisone are reported. The literature on this form of therapy is reviewed.

It may be deduced from this review that cortisone or corticotrophin can be a life-saving drug in the acute fulminating attack of dermatomyositis, and in such a case the effect when it occurs is very dramatic. The drug usually fails to improve the more chronic form of the disease, but in view of the occasional success claimed in this category it should never be withheld. Likewise, in dermatomyositis associated with neoplasm a curative effect of the former process by the hormones has been described.

The first report of the treatment of acute dermatomyositis by corticotrophin was published in 1949 by Elkinton and his colleagues; it described the case of a moribund 5-year-old boy suffering from the disease which remitted after a four-weeks course of corticotrophin, following on two shorter unsuccessful trials. Thorn *et al.* (1950), in their paper on corticotrophin and cortisone, mentioned three cases, in two of which improvement occurred. This was not sustained according to Wedgewood *et al.* (1953), who described 10 cases and concluded that a cure by these hormones may be expected in the acute case only.

The following three instances demonstrate success and failure from the use of corticotrophin in this condition.

McElligott, Br Med J, 1956; 2(5008): 1509-11

Patterns of Polymyositis and Their Responses to Treatment

CARL M. PEARSON, M.D., F.A.C.P., *Los Angeles, California*

TREATMENT PROGRAM

Therapeutic trials in polymyositis have, over the years, been many and varied (13). Prior to the discovery of adrenocorticotrophic hormone and the corticosteroids, none of the previous treatments had any noticeable or consistently beneficial effect upon the course of the disease. Now that sufficient experience has been obtained with the use of the various corticosteroids in these conditions, it seems definite that the natural course of the disease can be satisfactorily altered in many cases. Also, suppression of the disease process is possible in most so that the previous prediction of the over-all mortality rate of 50 per cent (3) can be sharply reduced.

Four points are worthy of emphasis concerning corticosteroid therapy in polymyositis: [1] the earlier the treatment is begun after the appearance of clinical symptoms, the more favorable the outcome; [2] the various types of polymyositis, as classified herein, may respond differently to corticosteroid therapy, both in regard to the rate of improvement and to its eventual completeness; [3] careful and prolonged follow-up care is necessary in all cases; and [4] in the presence of malignancy, corticosteroid therapy is likely to only partially benefit the myopathy and to lose its effectiveness altogether as the malignancy advances.

Pearson, Ann Intern Med, 1963; 59: 827-38

TREATMENT

Over the years many agents were tried in the treatment of polymyositis, without significant benefit. With the advent of ACTH and the various corticosteroids, the natural course of the disease has been altered and satisfactory suppression is possible in most cases. We believe that every patient with acute polymyositis should receive corticosteroids. The initial dosage in adults should be 50 to 60 mg prednisone in three or four divided daily doses. In some children and in adults with coexistent malignancy or Sjögren's syndrome, the response will be poor or only temporarily good. In almost all other patients it will be gratifying. Within the past several years a

Pearson, in Arthritis and Allied Conditions, 1979

IMMUNOSUPPRESSIVE THERAPY

There are a number of cases of any type of polymyositis or dermatomyositis that may not respond to corticosteroids, even in full doses over a long period of time. Because of this, and because some cases of polymyositis may represent examples of altered immune response or an autoimmune response, Malaviya and associates successfully used intermittent high-dose intravenous methotrexate in four patients with dermatomyositis, three of whom had recently proved to be refractory to corticosteroids.[54]

Pearson, in Arthritis and Allied Conditions, 1979

TREATMENT OF DERMATOMYOSITIS WITH METHOTREXATE

ANAND N. MALAVIYA
M.D. Lucknow

AMIRA MANY
M.D. Jerusalem

ROBERT S. SCHWARTZ
M.D. New York

From the Clinical Immunology Service, New England Medical Center Hospitals, and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts

Summary Four patients with dermatomyositis were treated with intravenous methotrexate. Three of them were refractory to corticosteroids, and one had received no other treatment. Each patient was bedridden by severe muscular weakness before treatment, and one was in the terminal phases of the disease. All patients responded to methotrexate with improvement of muscular strength to normal or near-normal and disappearance of the rash. Concomitantly, laboratory abnormalities indicative of muscle disease disappeared.

Malaviya et al., Lancet 1968; 2: 485-8

What needs to be treated?

- Be clear about the goals of therapy
  - Weakness
  - Rash
  - Shortness of breath
  - Swallowing trouble
  - Inflammatory arthritis
  - Raynaud’s
  - Pain
  - Fatigue

Core Set Measures for Myositis

- Muscle strength
- Physical function
- Patient global assessment
- Physician global assessment
- Muscle enzymes
- Extra-muscle activity

Rider, et al, J Rheum 2003; 30: 603-17

Approach to Management of Myositis

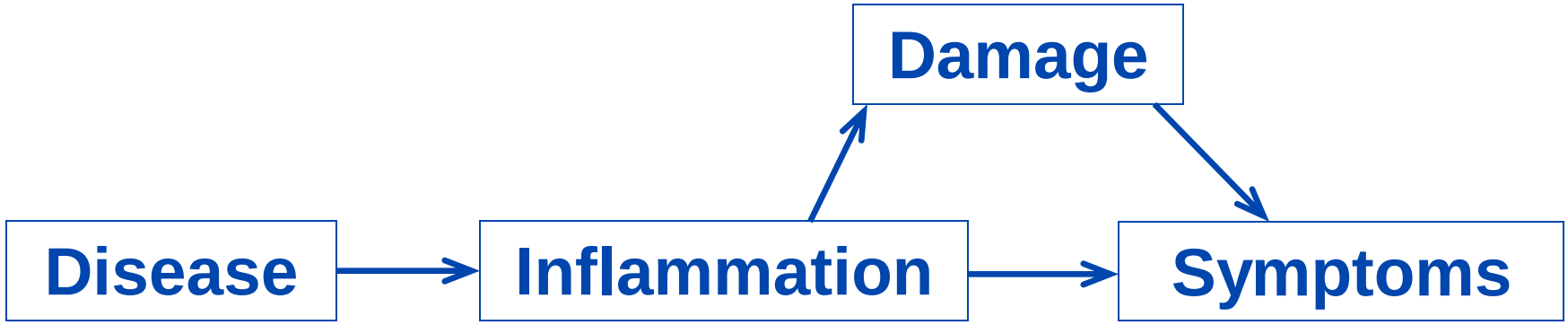
Treat underlying process

Immuno-suppressives

Corticosteroids

Directed therapies

Approach to Management of Myositis



Treat underlying process

Immuno-suppressives

Corticosteroids

Directed therapies

My Approach to Prednisone

- Begin 1 mg/kg/d (usually max 80 mg/d)
- Continue 1 month
- 2 weeks each:
  - 40 mg/d
  - 30 mg/d
  - 25 mg/d
  - 20 mg/d
  - 17.5 mg/d
  - 15 mg/d
  - 12.5 mg/d
- 10 mg/d and then decide what next

My Approach to Immunosuppressives

First-line agents
- Methotrexate
- Azathioprine (Imuran)
- Mycophenolate mofetil (CellCept)
- Hydroxychloroquine (Plaquenil) – DM

Studies
- Tocilizumab (Actemra)
- Belimumab (Benlysta)
- Abatacept (Orencia)

Second-line agents
- IVIg
- Rituximab (Rituxan)
- Tacrolimus (Prograf)
- Cyclosporine A (Neoral, Sandimmune)
- Leflunomide (Arava)

Severe disease
- Cyclophosphamide (Cytoxan)

Never used
- ACTHAR gel

Other Things to Remember

- Osteoporosis
- Pneumocystis prevention
- Immunizations

IVIg Recommendations from Various Expert Groups

Disorder	AAN recommendation	EFNS recommendation	UK NHS recommendation
Dermatomyositis	May be considered for non-responsive patients Level C	Second-line treatment Level B	Appropriate for resistant or aggressive disease Level B
Inclusion body myositis	Insufficient evidence Level U	Not recommended Level A	Appropriate for resistant or aggressive disease Level B

- AAN – American Academy of Neurology
- EFNS – European Federation of Neurological Societies
- UK NHS – United Kingdom National Health Service
- Recommendations based on level of evidence
  - A: Established
  - B: Probable
  - C: Possible
  - U: Insufficient

Hughes & Lunn, Nat Rev Neurol 2012; 8: 303-5

Endurance Exercise in PM and DM

- Randomized, controlled trial, n = 21
- 12-week endurance exercise
  - 1 hr, 3 x/week – cycling 30’, 20’ knee extensors
  - 2x/week supervised, 1x/week at home
- Control – no change in exercise program
- Improved:
  - Physical function and vitality on SF-36
  - ADL score, strength
  - $V0_2$ max
  - Disease activity (7/11 vs. 0/10)

Munters et al, Arthritis Care Res 2013; 65: 1959-68

Resistive Home Exercise in PM and DM

- Randomized, controlled trial, n = 19, early active
- Exercise group – with phone support
  - 12 weeks, 5x/week, resistive home exercise and brisk walking
  - 12 weeks, 2x/week home or gym exercise
- Control group – 15' range of motion and usual walks
- Findings:
  - Improved muscle performance & aerobic capacity, both groups
  - Safe – no increase CK or inflammation on biopsy

Alexanderson et al, J Rheumatol 2014; 41: 1124-32

Exercise for Myositis

- 8 patients (5 DM, 3 PM)
- 7 week resistance exercise program
- Muscle biopsies pre- and post-
- Strength improved
- VO_{2max} improved

Nader et al, Mol Med 2010; 16: 455-64

Exercise for Myositis

Gene transcript changes in muscle

- Inflammation
  - Downregulation of proinflammatory genes
  - Upregulation of antiinflammatory genes
- Fibrosis
  - Downregulation of profibrotic genes
  - Upregulation of antifibrotic genes
- Other
  - Upregulation of oxidative metabolism genes
  - Downregulation of lipid biosynthesis genes

Nader et al, Mol Med 2010; 16: 455-64

The Future

- Better definitions of the disorders and ability to separate them
- Better ways to evaluate how patients are doing
- Better understanding of pathogenesis
  - What genes are important?
  - What triggers the diseases?
  - What are the mechanisms?
- Better treatment or prevention

Questions?