



New England Society of Allergy
Fall Meeting

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RHEUMATOLOGY FOR THE ALLERGIST

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DISCLOSURE

- During the past 12 months, neither I nor my family have any relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.



Special Acknowledgment To



*The Samara Jan Turkel Clinical Center
For Pediatric Autoimmune Disease*

OBJECTIVES

- Describe the rheumatologic approach to medicine and how this might inform treatment of allergic conditions
- Discuss the most common rheumatologic issues likely to be faced by an allergist

PEDIATRIC RHEUMATOLOGY

THE STUDY OF INFLAMMATION OR
PAIN IN MUSCLES, JOINTS, OR
FIBROUS TISSUES OF CHILDREN

RECENT RHEUMATOLOGIC HEADLINES

- *Anti-Cytokine Therapy Changes Face of Rheumatology*
- *Microarray Analysis Demonstrates IFN Signature at Root of SLE*
- *Stem Cells may Revolutionize Care of Degenerative Arthritis*

THE REAL STORY

The real foundation of rheumatology is history and physical:

- When are symptoms worse?
- What makes them feel better? Worse?
- What is the nature of the discomfort

Answers to these questions will yield a presumptive diagnosis in ~85% of cases!

OVERVIEW: LESSONS FROM RHEUMATOLOGY

1. History and Physical Exam are still the basis of clinical medicine
2. As with any foreign language, the basic vocabulary needed to survive in rheumatology is small
3. Preventing morbidity is more effective than treating it

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MOST OF WHAT HURTS IS NOT ARTHRITIS...

414 referrals to a pediatric rheumatology practice
226 with chief complaint of musculoskeletal pain:

- Diagnoses: hypermobility, overuse syndromes, psychogenic pain
- Only 20/226 (9%) had arthritis

PAIN is the strongest negative predictor of inflammatory disease

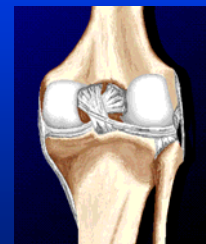
McGhee et al., *Pediatrics* 2002;110:354.

TIMING OF SYMPTOMS

	A.M.	P.M.	NIGHT TIME	ACTIVITY
INFLAMMATORY	+++	+	-	IMPROVES
MECHANICAL	+/-	++	+/-	WORSENS
BONY	++	++	++	NO CHANGE
NEUROPATHIC	+	++	+++	NO CHANGE

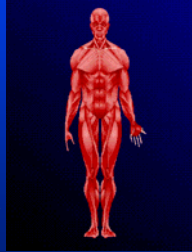
INFLAMMATORY

- WORSE IN A.M.
- MORNING STIFFNESS
- IMPROVES WITH ACTIVITY
- TYPICAL OF ARTHRITIS



MECHANICAL PAIN

- WORSE AFTER ACTIVITY
- WORSE AT END OF DAY
- MAY BE DUE TO OVERUSE, SPRAINS, ETC.



BONY PAIN

- CONSTANT
- NO CHANGE WITH ACTIVITY
- MAY BE DUE TO INFECTION, TRAUMA, TUMOR



RULING OUT MALIGNANCIES

- NATURE OF PAIN
 - Constant, awakens at night
- LOCATION OF PAIN
 - Periarticular or unlocalized
- ASSOCIATED FINDINGS
 - Abnormal CBC
 - Cytopenias
 - Radiographic changes

NEUROPATHIC PAIN

- WORST AT NIGHT, RECUMBENT
- NO CHANGE WITH ACTIVITY
- BURNING QUALITY
- MAY HAVE ALLODYNIA ASSOCIATED



NON-ORGANIC PAIN

- CHARACTERISTIC FEATURES
 - EXAGGERATED DESCRIPTIONS OF PAIN
 - DISORDERED SLEEP PATTERNS
 - EXTENSIVE PERIODS OF SCHOOL ABSENCE
 - MULTIPLE POORLY DEFINED SOMATIC COMPLAINTS
 - MULTIPLE PHYSICIANS OR CONSULTATIONS

JRA: PRESENTATION

- SWOLLEN, TENDER JOINTS
- LIMP / REGRESSION OF MILESTONES
- MORNING STIFFNESS
- WORSENS WITH COLD, DAMP, OR HUMID WEATHER
- NOT PAINFUL

RHEUMATOLOGIC PHYSICAL EXAM

- **OBSERVATION IS MOST SENSITIVE TOOL OF EXAMINATION**
- **PALPATION NOT USEFUL IF NOTHING HURTS**
- **PATHOLOGY AFFECTS EXTREMES OF RANGE OF MOTION FIRST**

LESSONS FROM RHEUMATOLOGY

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BASIC VOCABULARY OF (PEDIATRIC) RHEUMATOLOGY

1. ANA
2. ELEVATED ACUTE PHASE REACTANTS
– ESR, CRP
3. HLA B27
4. RHEUMATOID FACTOR
5. LYME SEROLOGIES
6. BONE SCAN

POSITIVE ANA's IN CHILDHOOD

- | | |
|--|---|
| <ul style="list-style-type: none"> • CHUDWIN et al (1983) <ul style="list-style-type: none"> – 1972 - 1982 – 138 children < 18 – ANA's > 1:20 – 70% with <i>AUTOIMMUNE DISEASE</i> | <ul style="list-style-type: none"> • CABRAL et al (1992) <ul style="list-style-type: none"> – 1981 - 1988 – 108 children with MSK pain – ANA > 1:20 in 24 – + ANA persisted in 21 / 24 (mean 39 mos) – <i>NO AUTOIMMUNE DISEASE</i> |
|--|---|

POSITIVE ANA's IN CHILDHOOD *

DIAGNOSIS	PERCENTAGE	MEAN ANA TITER	ANA RANGE
SLE	27 %	1:382	1:80 - 1:1280
JRA	24 %	1:133	1:40 - 1:320
OTHER CTD	14 %	1:317	1:80 - 1:2560
SUSPECTED CTD	20 %	1:273	1:20 - 1:640
PRESUMED VIRUS	8 %	1:213	1:80 - 1:320

* Chudwin et al, Am J Dis Child 1983; 137:1103-1106

BASIC UTILITY OF ANA

1. **WHOLLY DEPENDENT ON CLINICAL SETTING**
2. **TITERS \geq 1:640 LIKELY INDICATE PATHOLOGY *per se***
3. **NOT USEFUL FOR FOLLOWING DISEASE ACTIVITY**
4. **SPECIFIC ANTIBODY PATTERN OF SECONDARY CONCERN**

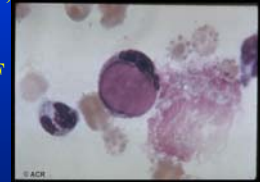
ANA TESTING*

ANA titer	Relative Risk	LIKELIHOOD OF DISEASE	
		Primary Care Setting	Referral Clinic
>1:1280	9.9	17%	81%
1:640	2.2	4.2%	49%
1:320	1.1	2.1%	32%
1:80-160	0.8	1.6%	26%
≤1:40	<0.8	0.8-1.4%	15-23%

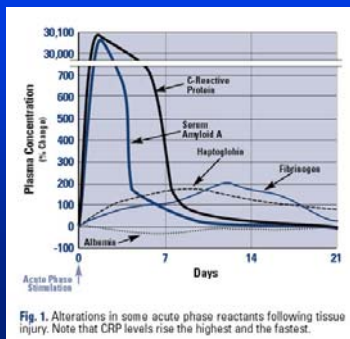
*Malleon PN et al, Arch Dis Child 1997; 77:199-304

MORE ON THE ANA

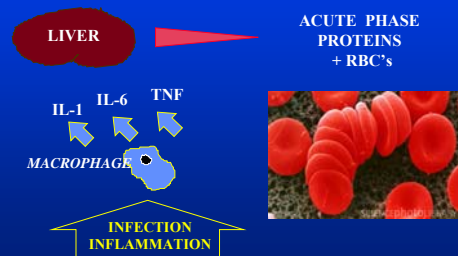
- ANA CHARACTERISTIC, NOT DIAGNOSTIC, OF AUTOIMMUNITY
- HIGH PERCENTAGE OF "FALSE" POSITIVES
 - 2% of children
 - 50% of adults over 80
- LE CELL TEST OBSOLETE



ACUTE PHASE REACTANTS



ERYTHROCYTE SEDIMENTATION RATE

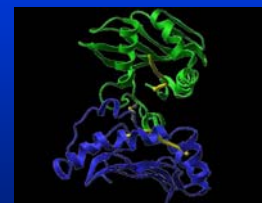


FACTORS AFFECTING ESR

- **SERUM PROTEINS**
 - Ig's, acute phase proteins
 - Net effect of production vs. consumption/loss
- **RED BLOOD CELLS**
 - Dependent on shape, charge, number
- **TIME COURSE**
 - Delayed response
 - Delayed normalization

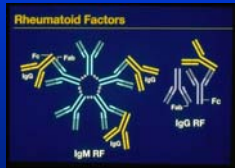
HLA B27

- **POSITIVE IN ~ 9% OF CAUCASIANS**
- **POSITIVE IN ~ 90% OF CASES OF ANKYLOSING SPONDYLITIS**
- **NOT PRESENT IN AFRICANS**
 - But incidence of AS similar to Caucasians
- **MAY INTERFERE WITH OBTAINING LIFE OR HEALTH INSURANCE**



RHEUMATOID FACTOR

- **AUTOANTIBODY**
- **CHARACTERISTIC OF ADULT RA**
- **RARE IN CHILDREN**
 - Measure of prognosis in polyarticular JRA
 - False positives:
 - Serum sickness, SBE
- **THEREFORE, DO NOT TRY AT HOME!**

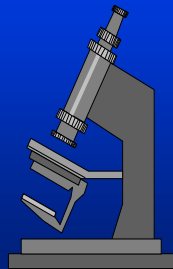


LYME DISEASE IN CHILDREN

- **Diagnosis:**
 - Clinical findings consistent with Lyme disease
 - Early: flu-symptoms
 - Late: arthritis
 - ELISA should be positive
 - Western blot: 2 IgM or 5 IgG bands
- **Prognosis: generally excellent**

LYME DISEASE: SERODIAGNOSIS

- **IMMUNOBLOT**
 - Appropriate controls
 - High-titer positive
 - Weak positive
 - Negative
 - IgM and IgG necessary for diagnosis of early Lyme
 - IgM very non-specific
 - IgG diagnostic with ≥ 5 bands



EXTREMITY COMPLAINTS: BONE SCAN

- **Flow phase: increased or decreased blood flow**
- **Static phase: increased uptake of Tc^{99m} -pyrophosphate**
- **Quantifies osteoblast activity**
- **Cannot replace history and PE**
- **Cannot localize site of unexplained extremity complaints**

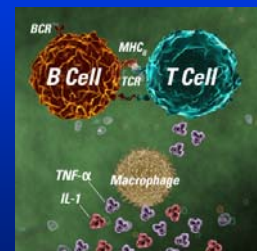


LESSONS FROM RHEUMATOLOGY

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BASIC PARADIGM – 1

Symptoms and end organ damage in allergic and rheumatologic conditions are mediated by inflammation.



BASIC PARADIGM - 2

Persistent low-grade inflammation may promote resistance to therapies



BASIC PARADIGM - 3

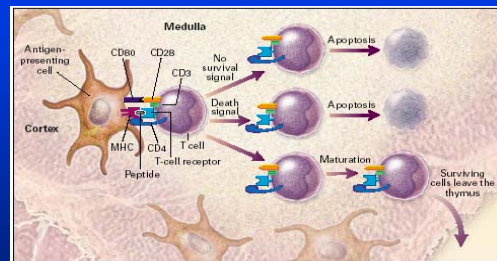
Early, aggressive therapy of inflammatory disorders will improve outcomes



THEORIES OF PATHOGENESIS: GENETIC FACTORS

If your father has no children and your grandfather has no children, then you probably won't have any children, either.

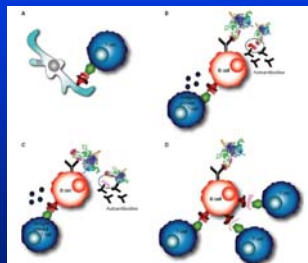
DEVELOPMENT OF AUTOIMMUNITY



- Autoimmune diseases begin as response to single antigen (Marrack P, Kappler J, Kotzin BL, Nat Med 2001; 7:899-905).

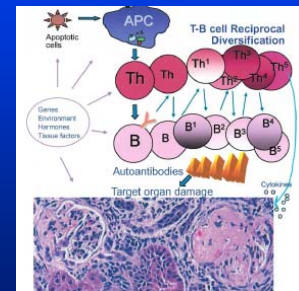
PROGRESSION OF AUTOIMMUNITY

- As disease progresses and becomes chronic, immune response broadens ("epitope spreading")



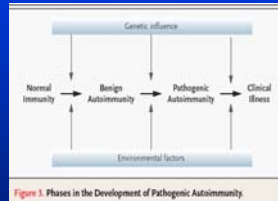
EPITOPE SPREADING IN AUTOIMMUNE DISEASES

- Epitope spreading enhances efficiency of protective immune response in clearing infections and tumors
- Epitope spreading in autoimmunity may cause generalization of process and loss of responsiveness to treatment

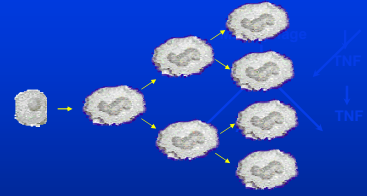


PROGRESSION OF AUTOIMMUNITY

- Severity of clinical illness worsens as immune response broadens and diversifies



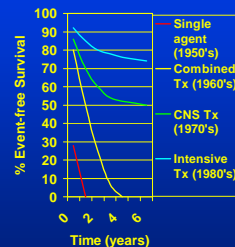
ANALOGY TO PROLIFERATIVE CONDITIONS



Malignant (self-reactive) clones divide, increasing load of 'disease cells' and overwhelming control mechanisms.

EFFECTS OF TREATMENT: ALL

- Improved outcomes related to first order kinetics of chemotherapy
 - For given therapy, constant fractional reduction of cells
 - In mice, single leukemic cell causes death
- Thus, malignant clones must be eradicated



OUTCOMES IN ALL

- Risk factors for poor prognosis in ALL
 - Gender
 - Age
 - WBC count
 - Organ infiltration
- BUT, effect of treatment strongest factor

Donadieu J et al. Critical study of prognostic factors in childhood ALL: Differences in outcome are poorly explained by the most significant prognostic variables. French Acute Lymphoblastic Leukemia study group. British J Haematol 1998; 102(3):729-739.

AUTOIMMUNE AND PROLIFERATIVE DISEASES: SIMILARITIES

- Both arise due to proliferation of cellular clones that have escaped immune surveillance
- Over time, pathogenic cells mutate/modulate making them more resistant to treatment
- "Minimal residual disease" leads to recurrence (Clinical significance of minimal residual disease in childhood ALL. Cave H et al, N Engl J Med 1998; 339(9):591-8)
- Restoration of tolerance / normal immune surveillance may equate with cure

AUTOIMMUNE AND PROLIFERATIVE DISEASES: DIFFERENCES

- Autoimmune conditions generally not fatal
- More than single 'malignant clone' required to perpetuate disease in autoimmune conditions (?)

WHY BE AGGRESSIVE?

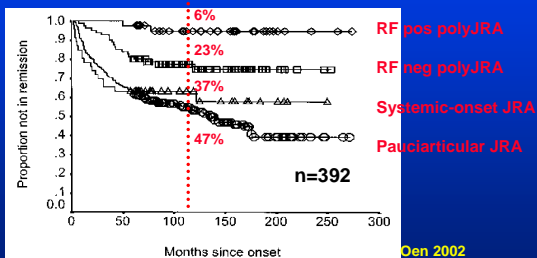
- Damage from autoimmune conditions generally irreversible, so it must be prevented to be avoided
- Responsiveness to therapy declines over time
 - “Window of opportunity” to treat (?cure) autoimmune diseases
- Evidence in many inflammatory conditions
 - Inflammatory arthritis
 - Juvenile Dermatomyositis

FUNCTIONAL OUTCOMES IN JRA

“Eighty percent of children can expect to be rid of inflammation when they reach adulthood.”

Canadian Arthritis Society, booklet on JRA for parents, 1991

DO KIDS REALLY OUTGROW JRA?



“remission” = no disease activity (on or off medications)

Courtesy of Peter Nigrovic, M.D.

DISEASE OUTCOMES IN JRA

Author (Yr)	Yrs follow-up (mean)	Active JRA at follow-up (%)
Laaksonen (1966)	16	41
Calabro (1976)	12	35
Hanson (1977)	10	55
Rennebohm (1984)	10	33
Levinson (1991)	18	45

JRA: THE GOOD NEWS

“Arthritis Sufferers Growing Younger”--
headline, Joplin (Mo.) Globe, Sept. 5, 2003

JRA: COMPLICATIONS

- LIMB LENGTH DISCREPANCY
- MUSCULAR ATROPHY
- JOINT CONTRACTURES
- GROWTH ARREST



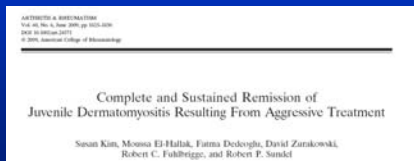
AGGRESSIVE THERAPY FOR ARTHRITIS

- **Adult RA: Early treatment of patients with new onset RA (< 1 year duration) with DMARD's vs. pyramid approach:**
 - Significantly higher complete response rate at 1 year of treatment (24% vs. 11%).
 - Significantly lower radiographic progression after two years
 - More patients with clinically relevant improvement at 5 years (74% vs. 63%)

FUNCTIONAL OUTCOMES IN JRA

Author (Yr)	Yrs follow-up (mean)	Class III/IV (%)
<i>Bunin (1959)</i>	10	31
<i>Jeremy (1966)</i>	18	24
<i>Hanson (1977)</i>	10	28
<i>Calabro (1989)</i>	25	15
<i>Levinson (1991)</i>	18	17

EARLY AGGRESSIVE THERAPY JUVENILE DERMATOMYOSITIS



JUVENILE DERMATOMYOSITIS

- **Rare inflammatory disorder of children**
 - Incidence 3 / 10⁶ children < 15 per year
- **Bohan & Peter criteria for diagnosis:**
 - Rash - Weakness
 - Myositis
 - Biopsy or EMG confirmation



JUVENILE DERMATOMYOSITIS

- **Traditional Therapy**
 - High-dose steroids
- **Outcomes**
 - 30% calcinosis
 - Chronic active disease
 - Mortality
 - 1960: 33% at 2 years
 - 2010: 1%



JDMS: EARLY AGGRESSIVE THERAPY

- 49 children with JDMS treated at CHB from 1994-2004
- Mean age at diagnosis 6.5 +/- 3.1 years
- Female:male = 26:23
- Treatment initiated mean of 5.2 months after onset
- Mean follow-up 48 +/- 30 months



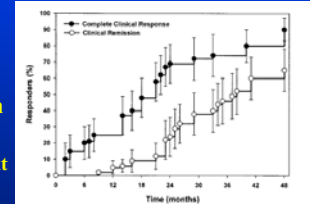
AGGRESSIVE JDMS THERAPY



- Oral prednisone + IVMP
- Add methotrexate if incompletely effective or steroid toxicity
- Add hydroxychloroquine for rash
- Cyclosporine, apheresis, IVIG for resistant cases
- Intensity therapy if ANY laboratory abnormalities persist

JDMS: RESULTS OF AGGRESSIVE THERAPY

- Complete clinical response 37/49 patients
- Clinical remission in 28/49 patients
 - No relapses over next 36 +/- 20 months



JDMS: RESULTS OF AGGRESSIVE THERAPY

- Calcinosis associated with longer time to onset of treatment, longer time to normalization of muscle enzymes
- Risk of calcinosis not related to demographics of specifics of therapy (e.g. number of doses of IVMP, age, etc.)

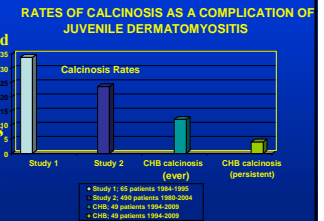
Table II. Comparison of patients with and without calcinosis

	Calcinosis (N = 6)	No calcinosis (N = 43)	P value
Age at onset (mean years ± SD)	6.1 ± 2.1	8.8 ± 15.8	200
Months to treatment (mean ± SD)	33.6 ± 4.1	4.8 ± 7.6	0.03
CK (mean ± SD)	3444 ± 4888	4058 ± 5435	800
AKKase (mean ± SD)	27.3 ± 20.4	10.5 ± 79.5	400
IVMP (mean ± SD)	213.6 ± 82.1	287.7 ± 107	800
Months to normal enzymes (mean ± SD)	34 ± 8.1	12.6 ± 14.7	0.03
Months to remission (mean ± SD)	42.8 ± 18.1	22.2 ± 17.6	0.05
IVMP treatment (N/%)	6/100	22/77	600
Number of IMIP pulses received	6.6 ± 6.1	10.5 ± 11.8	400

* Fisher's exact P value.

JDMS: RESULTS OF AGGRESSIVE THERAPY

- Complications:
 - Stress fractures in 5
 - Hypertension in 3
 - Infections in 2 (rotavirus and diarrhea, axillary furuncle)
- No cases of diffuse calcinosis
- Six patients with calcinosis*
 - 4: Resolved
 - 2: Persistent and superficial



AGGRESSIVE TREATMENT OF JDMS

- More Effective
 - Higher remission rate
 - Less calcinosis
 - Sustained benefit
 - ? Restoration of tolerance
- Provided that ...
 - Zero toleration of active muscle inflammation



THE KEY: BALANCE

- Must weigh risks and benefits to determine when early, aggressive therapy is indicated
 - Benefits may be immediate, risks delayed
 - Data, especially concerning new agents, are incomplete
 - Family and MD do not necessarily weigh concerns equally



CONCLUSIONS -1

- PEDIATRICS IS A CLINICAL SCIENCE. PROTEOMICS, IMAGING, LAB TESTING, ETC. NOTWITHSTANDING, USE YOUR HEAD!



CONCLUSIONS -2

- IMAGING AND LABORATORY TESTING SUPPLEMENT AND CONFIRM THE DIAGNOSIS, THEY DO NOT MAKE IT



CONCLUSIONS - 3

EARLY, AGGRESSIVE THERAPY OF INFLAMMATORY DISORDERS OPTIMIZES OUTCOMES AND MAXIMIZES CHANCES OF ACHIEVING 'CURE'



WHAT CAN ALLERGISTS LEARN FROM RHEUMATOLOGISTS?

- Remember the clinical foundation of medicine
- Treat physiologically: target specific disease mediators
 - Every benefit of steroids may be achieved more specifically and safely with another drug
- Prevent damage rather than address sequelae
- Weigh risks and benefits of treatments carefully



RHEUMATOLOGY: TO FOXWOODS AND BEYOND

- PERIOD OF RAPID PROGRESS
- COMPLEXITY OF TREATMENTS AND MONITORING OF TOXICITY INCREASING DRAMATICALLY
- BASIC SCIENCE BEGINNING TO INFORM THERAPY OF AUTOIMMUNE DISEASES



NOT UNLIKE ALLERGY!



SIR WILLIAM OSLER:
THE KEY TO A LONG LIFE IS ACQUIRING A CHRONIC DISEASE AND TAKING GOOD CARE OF IT.