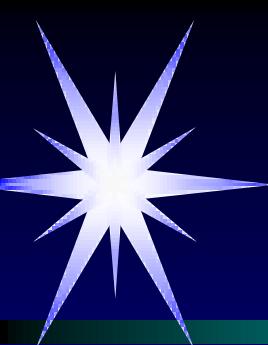




SYSTEMIC AUTOIMMUNE DISEASES: CLINICAL AND LABORATORY CHALLENGES FOR THE 21st CENTURY

Ricard Cervera, MD, PhD, FRCP
Department of Autoimmune Diseases
Hospital Clínic
Barcelona



AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

- ↗ 1. Great variety of conditions
- ↗ 2.
- ↗ 3.
- ↗ 4.
- ↗ 5.
- ↗ 6.
- ↗ 7.
- ↗ 8.
- ↗ 9.
- ↗ 10.



Classification of Autoimmune Diseases

ORGAN-SPECIFIC

Graves' disease

Addison's disease

ITP

Hashimoto's thyroiditis

IDDM

Pemphigus

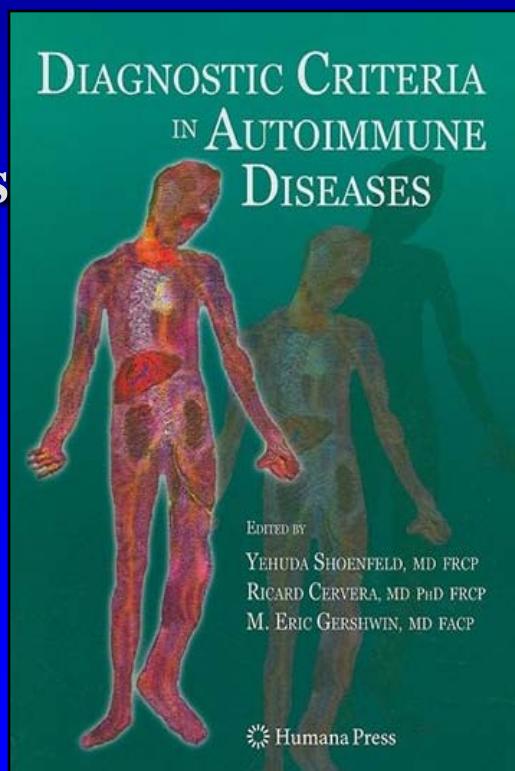
PBC

RA

Multiple sclerosis

Miasthenia gravis

103



SYSTEMIC

SLE

APS

Sjögren's syndrome

Systemic sclerosis

Systemic vasculitis

Dermato/Polymyositis

Behçet's disease

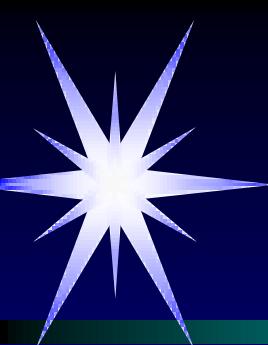
Mixed connective tissue disease



Autoimmune diseases:

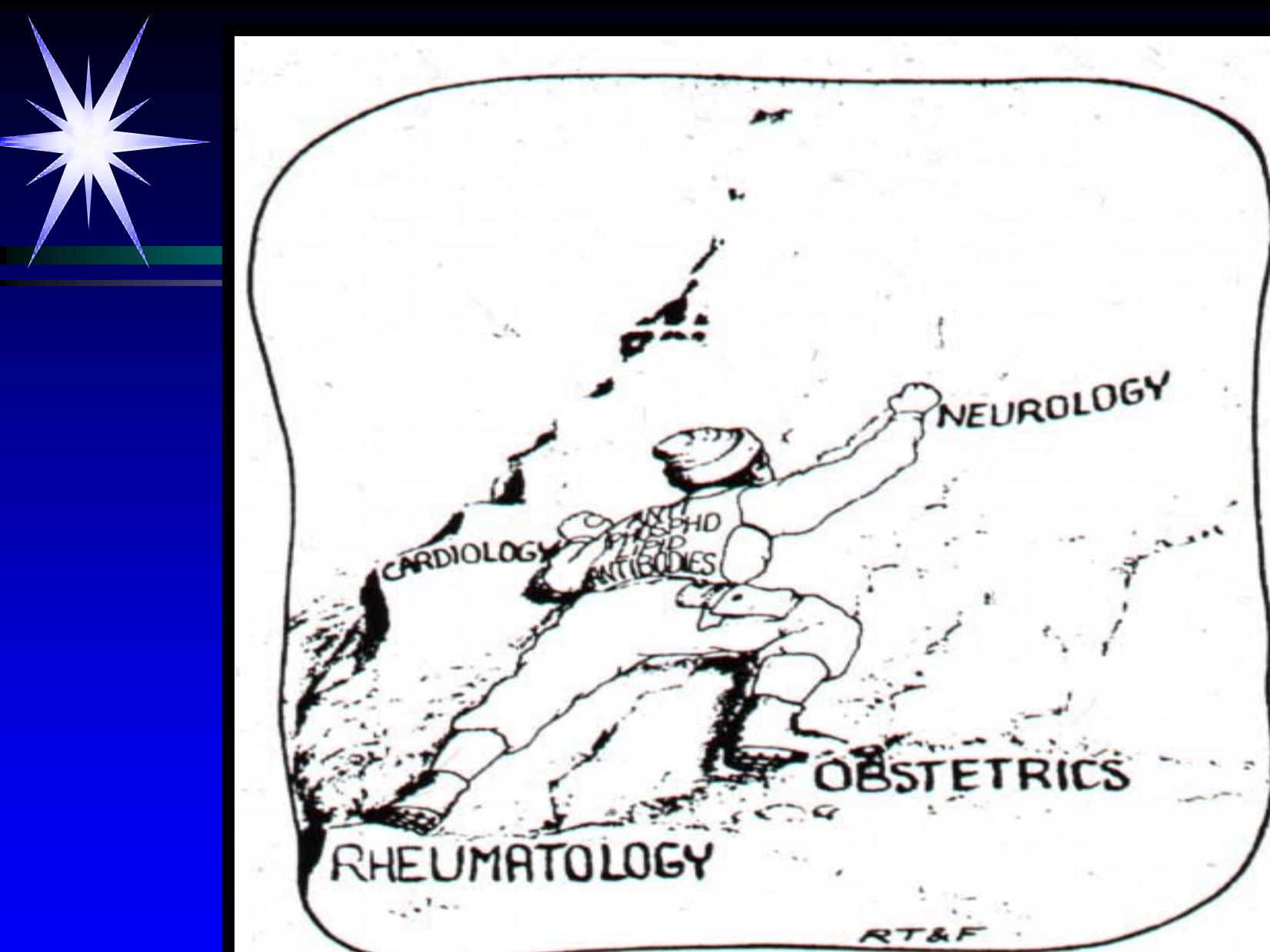
Estimated prevalence: 20%

NIH, 2001



AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

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Multidisciplinary Conditions

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CLÍNIC BARCELONA HOSPITAL UNIVERSITARI

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1-31-2000

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- [Clinical activities](#)
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- [Weekly Club on Autoimmune Diseases](#)
- [Weekly Club of the "Institut Clínic d'Infeccions i Immunologia"](#)
- [Ten Topics in Autoimmune Diseases and Rheumatology- 2003](#)

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Louise Coote Lupus Unit

What is Lupus?

Lupus is a disease in which the immune system becomes overactive. The normal immune system, which produces antibodies against foreign invaders, such as bacteria, goes into 'overdrive' and produces too many antibodies. It can affect any organ of the body.

It is often mistaken for other conditions, as the symptoms can be highly diverse, including:

- fatigue
- rashes
- allergies
- depression
- kidney failure.

Lupus

- ▶ [Lupus Unit](#)
- ▶ [Lupus pregnancy](#)
- ▶ [Lupus kidney](#)
- ▶ [Anti-phospholipid](#)
- ▶ [Lupus vasculitis](#)
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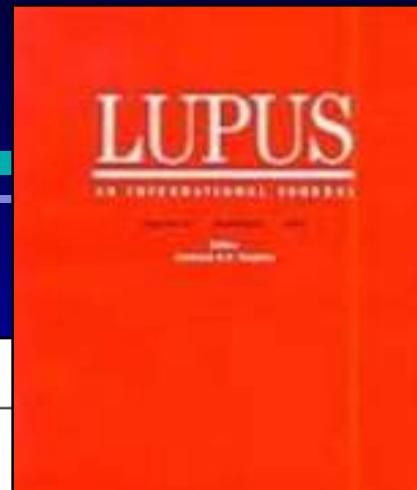
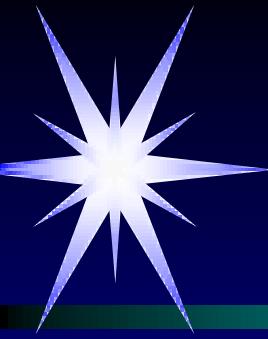
Division of Internal Medicine

Department of Internal Medicine B and Research Center for Autoimmune Diseases

The Department of Internal Medicine B, in addition to providing inpatient services to the general patient population, houses the Research Center for Autoimmune Diseases and treats patients with autoimmune conditions, especially Systemic Lupus Erythematosus (SLE).

Research Center for Autoimmune Diseases

Autoimmune diseases occur when the body tissues are attacked by the body's own immune system. These diseases primarily affect young people (an average age of 30 years), especially women of childbearing age. The Research Center for Autoimmune Diseases provides outpatient clinic services and maintains a world-class research institute and laboratory. The clinic specializes in the management of SLE and the Anti-Phospholipid Antibody Syndrome. The research center works to find the risk factors associated with autoimmune diseases and to establish better therapies for those afflicted with these conditions.



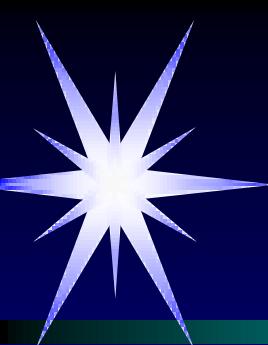
Lupus (2009) 00, 1–3
<http://lup.sagepub.com>

SPECIAL ARTICLE

Networking in Europe for special centres of excellence for autoimmune diseases

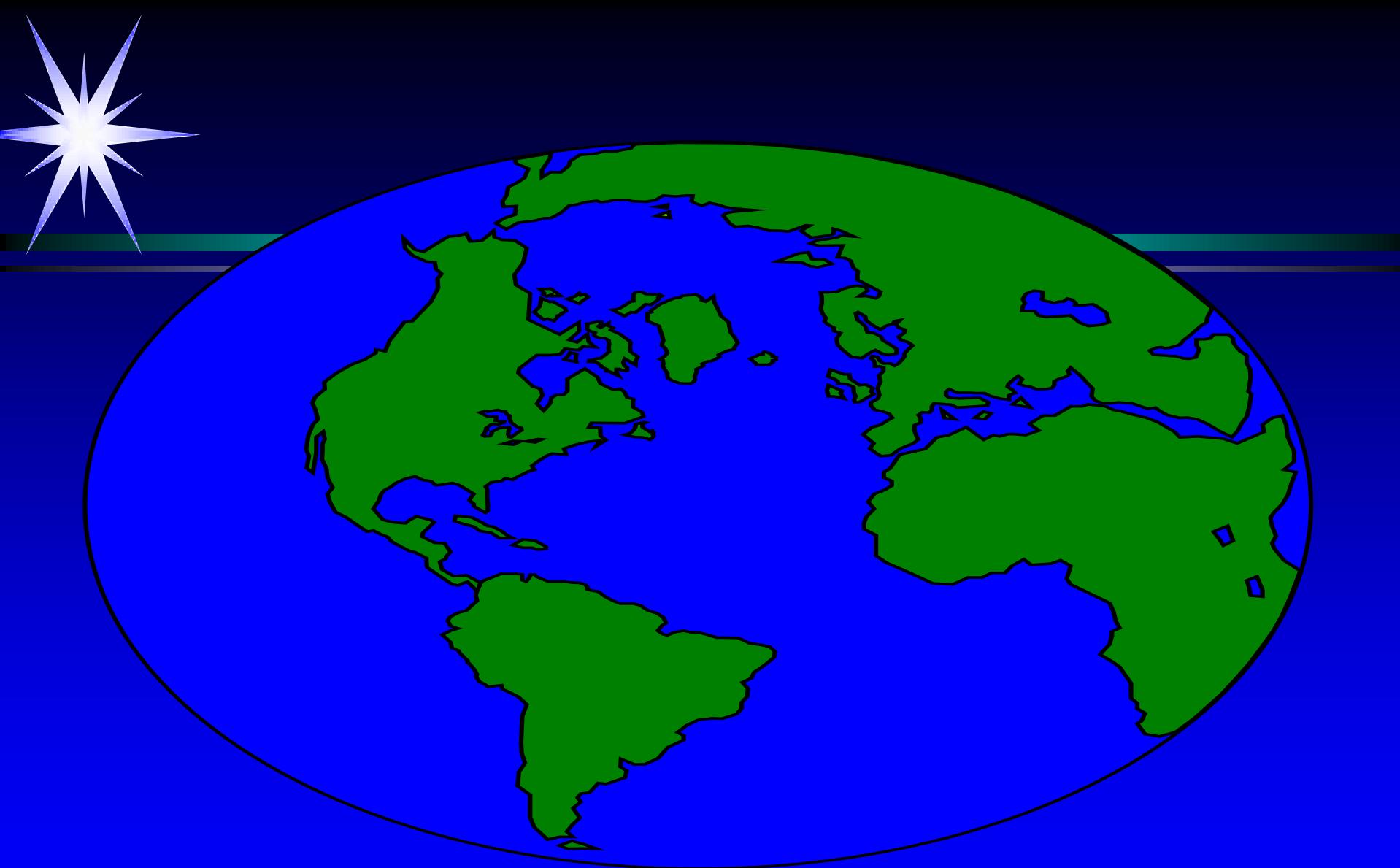
C Vasconcelos¹ and R Cervera²

¹Unidade de Imunologia Clínica, Hospital Santo António, Centro Hospitalar do Porto, Instituto Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal; and ²Department of Autoimmune Diseases, Hospital Clínic, Catalonia, Spain



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- ↗ 9.
- ↗ 10.



SLICC

Lupus (2001) 10, 375-377
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www.arnoldpublishers.com/journals

SPECIAL ARTICLE

The Systemic Lupus International Collaborating Clinics Group—origins and outcomes

DA Isenberg^{1*} and D Gladman on behalf of the SLICC group²

¹Centre for Rheumatology, Department of Medicine, University College London, London, UK; and ²Center for Prognosis Studies in Rheumatic Diseases, The Toronto Hospital, Toronto, Canada



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The GLADEL Multinational Latin American Prospective Inception Cohort of 1,214 Patients With Systemic Lupus Erythematosus: Ethnic and Disease Heterogeneity Among "Hispanics".

Medicine. 83(1):1-17, January 2004.
Pons-Estel, Bernardo A. MD; Catoggio, Luis J. MD; Cardiel, Mario H. MD, MSc; Soriano, Enrique R. MD; Gentiletti, Silvana MD; Villa, Antonio R. MD, MSc; Abadi, Isaac MD; Caeiro, Francisco MD; Alvarez, Alejandro MD; Alarcon-Segovia, Donato MD, PhD; on behalf of the Grupo Latinoamericano de Estudio del Lupus (GLADEL)

A stylized globe graphic focusing on Europe and the Mediterranean region, colored in green and blue.

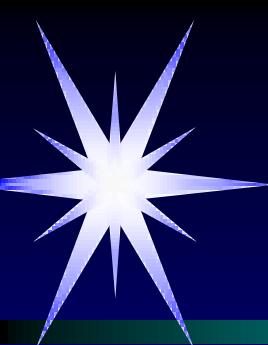
Euro-Lupus on Line

Official Web-site of the "European Working Party on Systemic Lupus Erythematosus"

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Euro-lupus

GLADEL



AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

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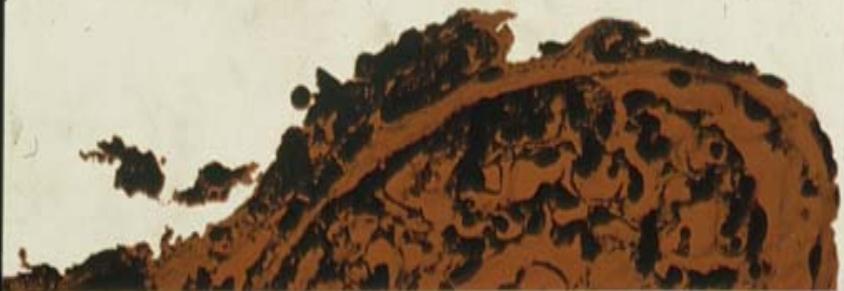


Systemic Lupus Erythematosus

Incidence: 5 new cases/100,000/year

Prevalence: 50 cases/100,000

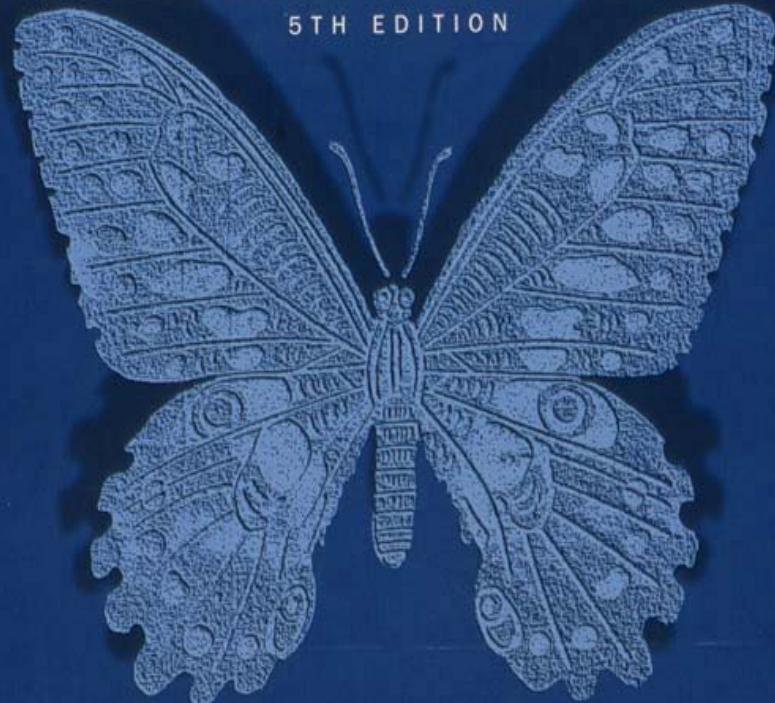
LUPUS ERYTHEM- ATOSUS



A review of the current status of Discoid and Systemic
Lupus Erythematosus and their variants. Edited by Edmund L. Dubois, M.D.

DUBOIS' LUPUS ERYTHEMATOSUS

5TH EDITION



**DANIEL J. WALLACE
BEVRA HANNAHS HAHN**
EDITORS

“EURO-LUPUS” PROJECT

2003

Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period

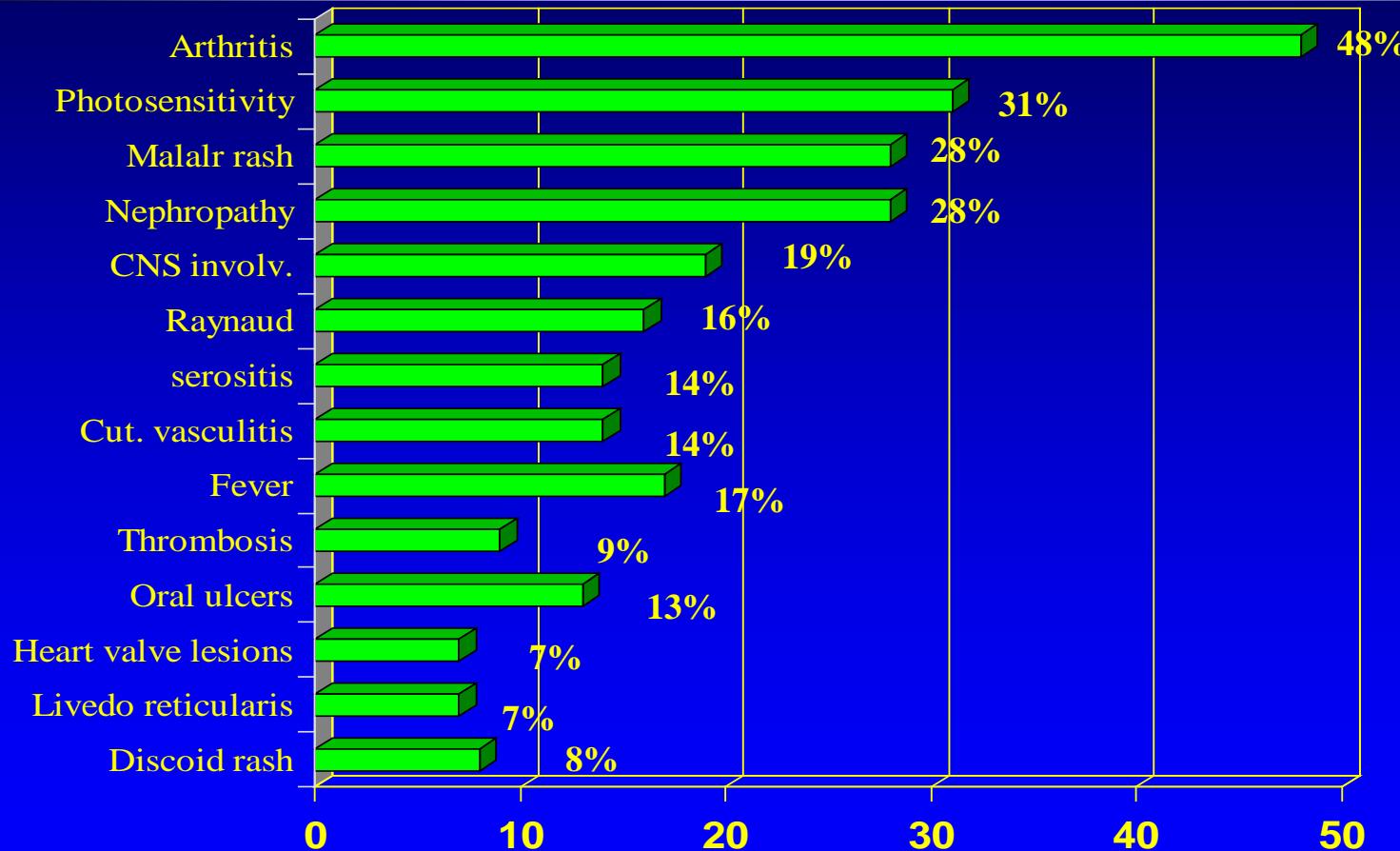
*A Comparison of Early and Late Manifestations in a Cohort of
1,000 Patients*

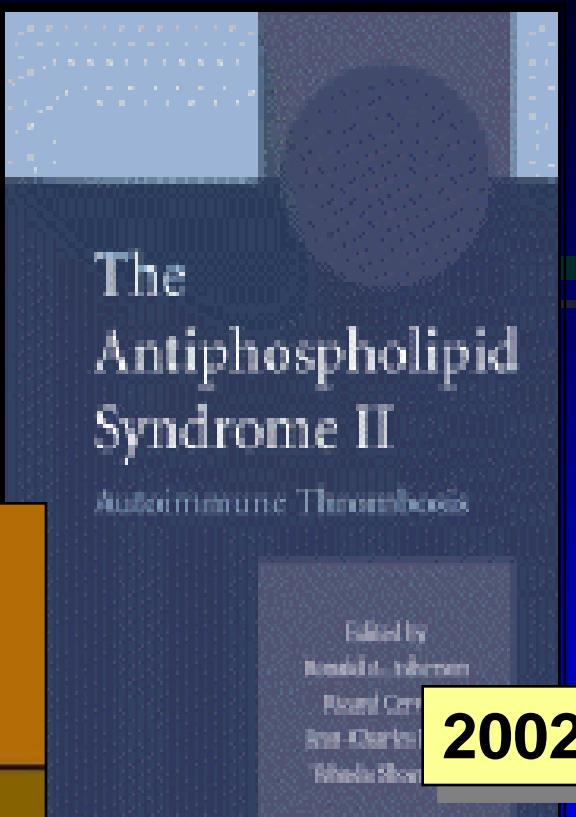
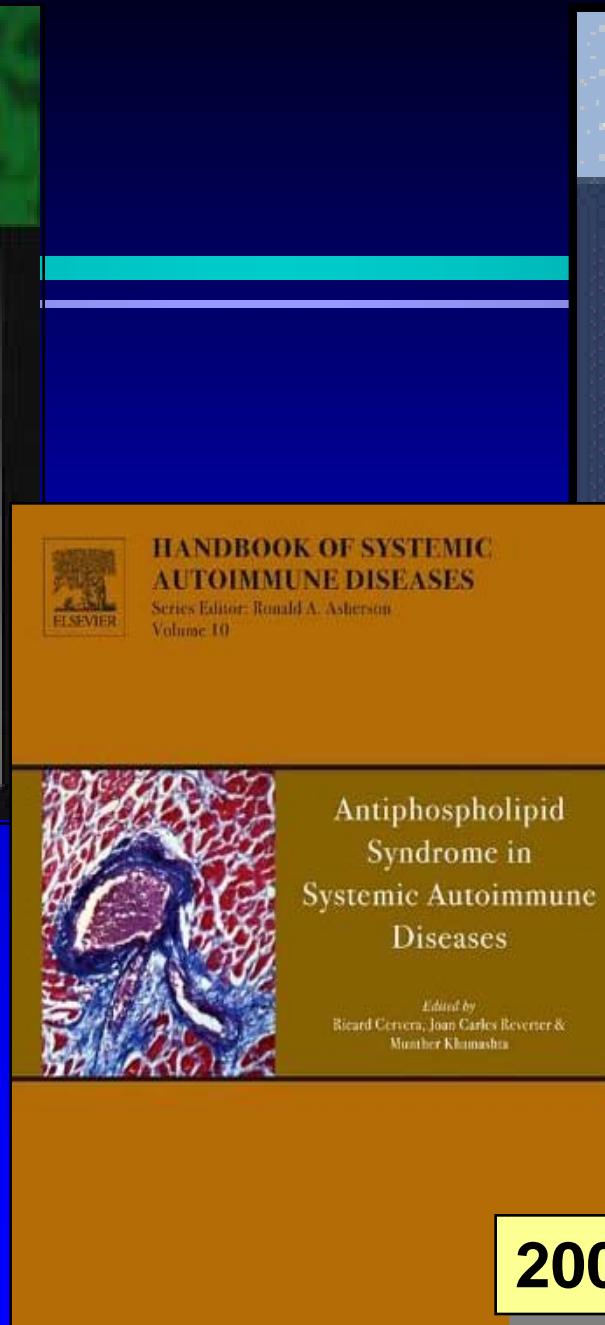
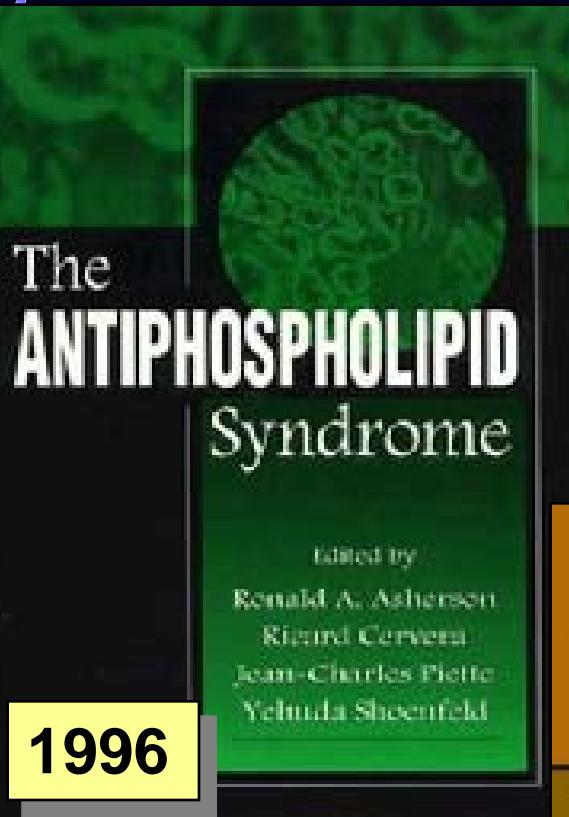
*Ricard Cervera, Munther A. Khamashta, Josep Font, Gian Domenico Sebastiani, Antonio Gil,
Paz Lavilla, Juan Carlos Mejía, A. Olcay Aydintug, Hanna Chwalinska-Sadowska, Enrique de Ramón,
Antonio Fernández-Nebro, Mauro Galeazzi, Merete Valen, Alessandro Mathieu, Frédéric Houssiau,
Natividad Caro, Paula Alba, Manuel Ramos-Casals, Miguel Ingelmo, Graham R.V. Hughes,
and the European Working Party on Systemic Lupus Erythematosus**

Medicine (Baltimore), 2003

PROYECTO “EURO-LUPUS”

Manifestaciones acumuladas (10 años)





“EURO-PHOSPHOLIPID” PROJECT

ARTHRITIS & RHEUMATISM
Vol. 46, No. 4, April 2002, pp 1019–1027
DOI 10.1002/art.10187
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2002

Antiphospholipid Syndrome

Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients

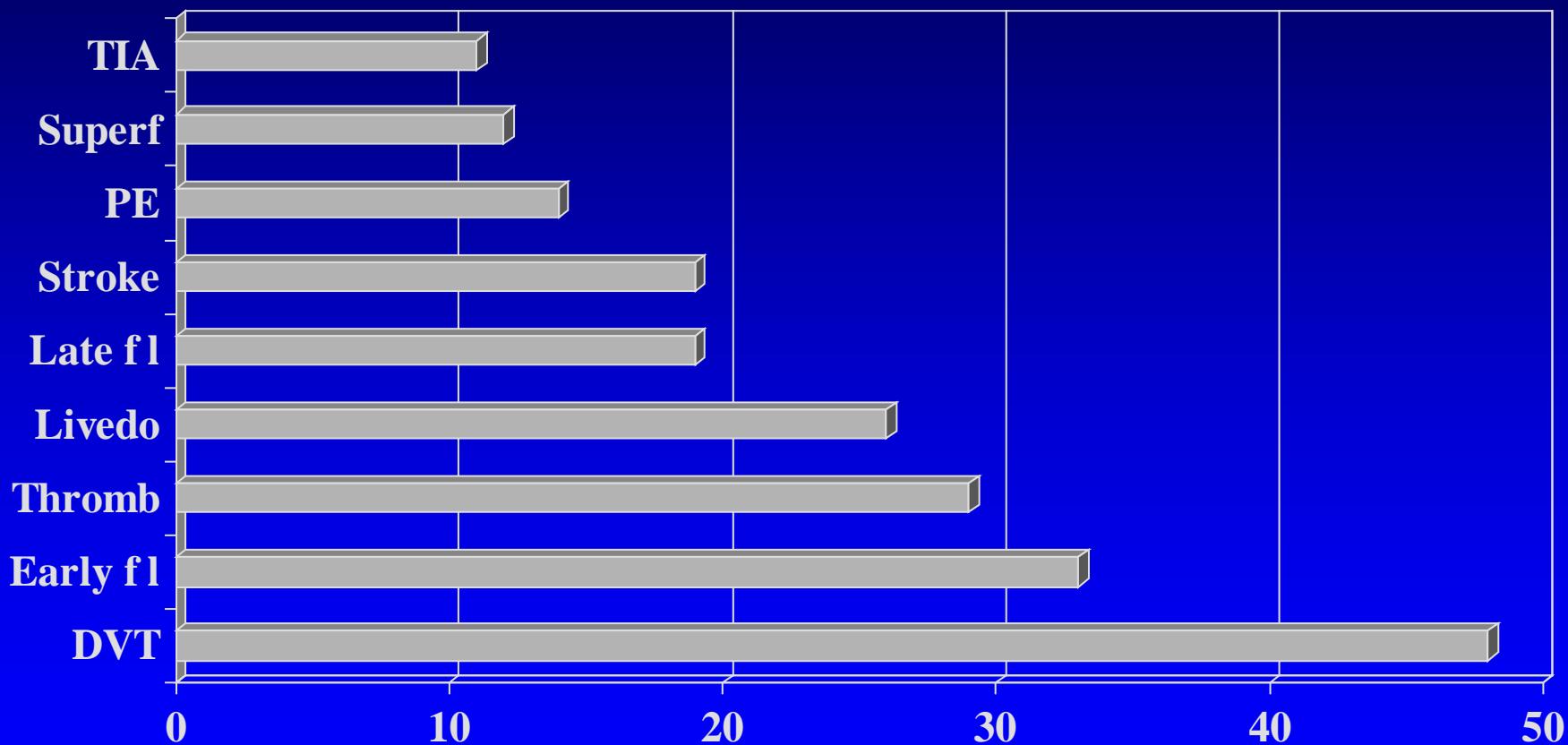
Ricard Cervera,¹ Jean-Charles Piette,² Josep Font,¹ Munther A. Khamashta,³ Yehuda Shoenfeld,⁴ María Teresa Camps,⁵ Soren Jacobsen,⁶ Gabriella Lakos,⁷ Angela Tincani,⁸ Irene Kontopoulou-Griva,⁹ Mauro Galeazzi,¹⁰ Pier Luigi Meroni,¹¹ Ronald H. W. M. Derkzen,¹² Philip G. de Groot,¹² Erika Gromnica-Ihle,¹³ Marta Baleva,¹⁴ Marta Mosca,¹⁵ Stefano Bombardieri,¹⁵ Frédéric Houssiau,¹⁶ Jean-Christophe Gris,¹⁷ Isabelle Quéré,¹⁷ Eric Hachulla,¹⁸ Carlos Vasconcelos,¹⁹ Beate Roch,²⁰ Antonio Fernández-Nebro,²¹ Marie-Claire Boffa,² Graham R. V. Hughes,³ and Miguel Ingelmo,¹ for the Euro-Phospholipid Project Group

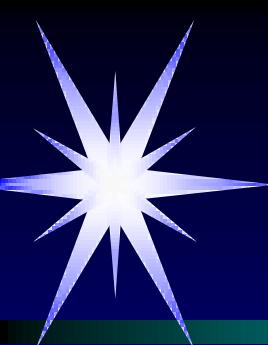
Arthritis Rheum, 2002



EURO-PHOSPHOLIPID PROJECT

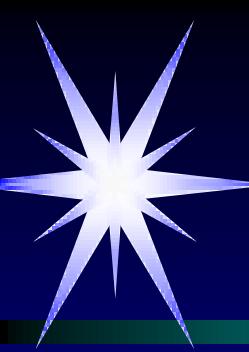
Cumulative manifestations





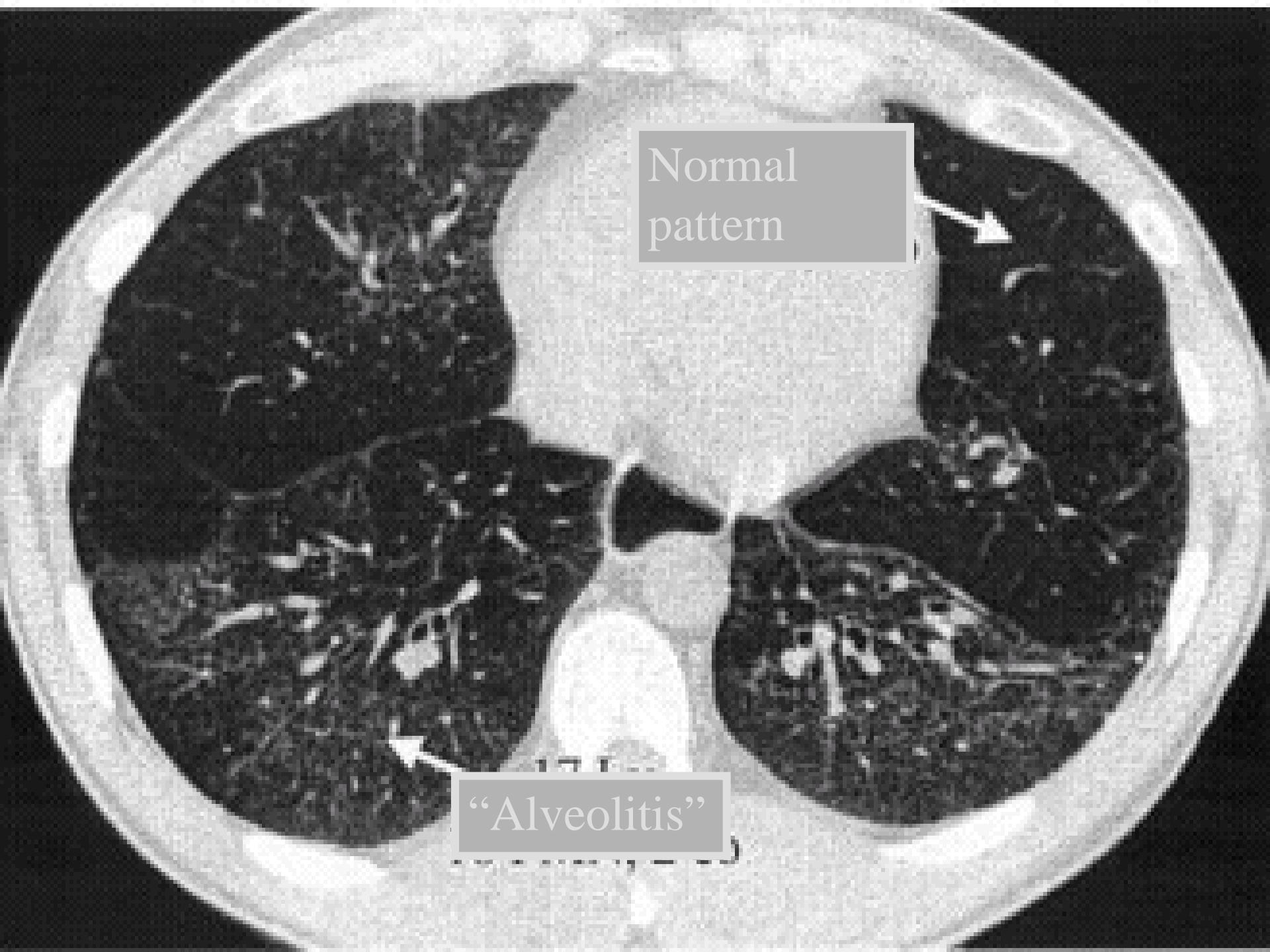
AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

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- ↗ 6.
- ↗ 7.
- ↗ 8.
- ↗ 9.
- ↗ 10.



Systemic sclerosis

- ↗ No therapy for sclerosis
- ↗ Therapy for inflammation



Normal
pattern

“Alveolitis”

Prednisolone orally at 20 mg/day – taper 15 mg at 4 weeks, 10 mg at 8 weeks
Cyclophosphamide – monthly IV pulses, start 400 mg/m² and titrate up to max of 800 mg/m² OR
– oral daily, start 0.5 mg/kg per day and titrate up to maximum of 1–2 mg/kg per day

monitor PFTs 3 monthly

Reassess at 6 months on basis of symptoms, repeat PFTs and HRCT

Deterioration despite adequate dose CYC

Intolerant of adequate dose CYC therapy

Stable or improved

Consider azathioprine
2.5 mg/kg per day+prednisolone

Continue prednisolone and CYC at same doses

Stop CYC and consider trial medication

Reassess at 12 months with repeat PFTs

Stable or improved

Continue prednisolone 7.5–10 mg/day
Consider reducing frequency of CYC pulses OR switching to azathioprine

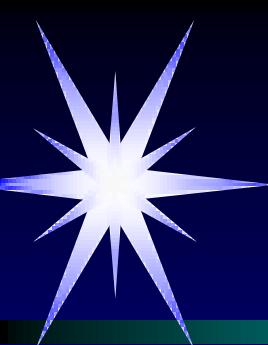
Reassess at 18 months with repeat PFTs

Stable or improved

Stop cytotoxics and monitor PFTs 3 monthly
Gradually wean prednisolone if stable
If PFTs fall with withdrawal of treatment,
consider recommending prednisolone +/- cytotoxic

PFT parameters to assess response

- FVC ≥10% improved
- FVC <10% deteriorated
- DLCO ≥15% improved
- DLCO <15% deteriorated



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HCV

MIXED
CRYOGLOBULINEMIA



MOLECULAR MIMICRY

Journal of Clinical Immunology, Vol. 24, No. 1, January 2004 (© 2004)

Antiphospholipid Syndrome Infectious Origin

M. BLANK, R. A. ASHERSON, R. CERVERA, and Y. SHOENFELD^{1,4}

J Clin Immunol 2004; 24: 12-23

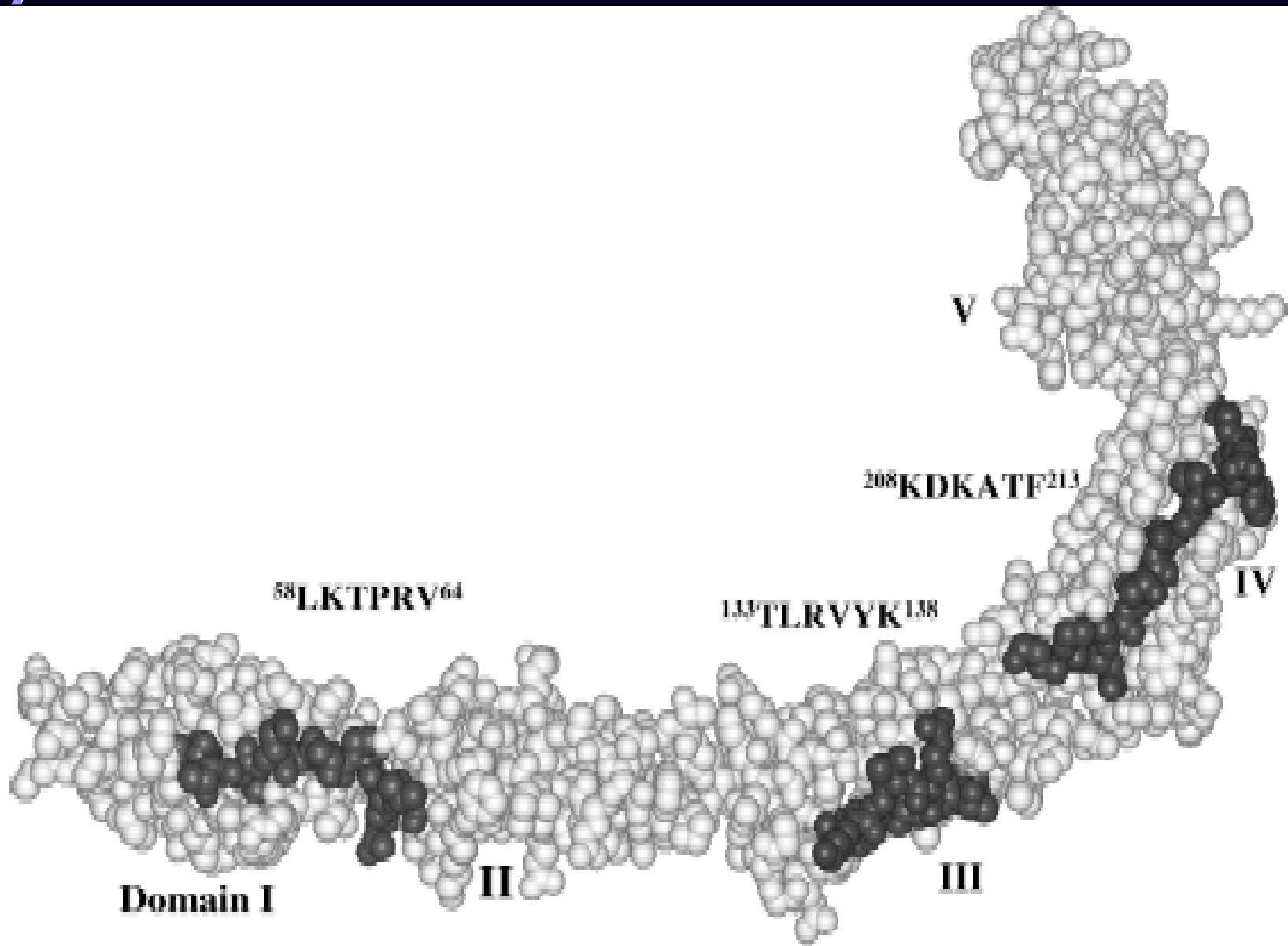
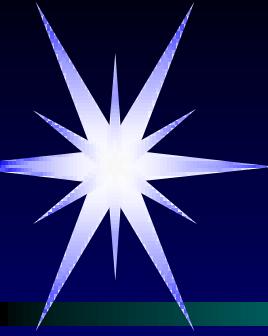


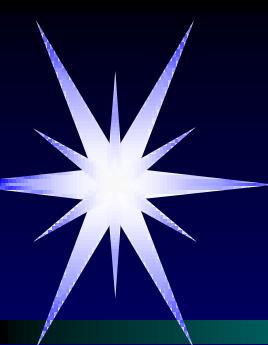
Fig. 1. Location of the β 2GPI-related peptides identified by the peptide phage display library.

Table III. Antiphospholipid Abs Detected in Diverse Infections and β 2GPI Peptide Homologies Shared with Structures in These Pathogens

| | Infections associated with circulating anti-PL Abs | TLRVYK (38) ^a | LKTPRV (38) | KDKATF (38) | GDKVSFF (49) | GRTCPKP- DDLP (53) |
|---|--|--------------------------|--------------------|--------------------|--------------|-----------------------|
| Viral | | | | | | |
| CMV | + | | | + | | + |
| EBV | + | | + | | | |
| HIV | + | | +2 ^b | | + | |
| Hepatitis C | + | | | | | |
| Parvovirus B19 | + | | | | | |
| Adenovirus | + | | | | + | |
| Varicella | + | | | | | |
| Vaccinia | + | | +2 | | | |
| Mumps | + | | | | | |
| Rubella | + | | | | | |
| HTLV-1 | + | | | | | |
| Herpesvirus | - | | | | | + |
| Bacterial | | | | | | |
| Leprosy | + | | | | | |
| Tuberculosis | + | | + | + | | |
| <i>M. pneumoniae, M. penetrans</i> | + | | | | | |
| <i>Salmonella</i> | + | | +, <i>typhi</i> | | | |
| Staphylococci | + | | + | + | + | |
| Streptococci | + | | +, <i>pyogenes</i> | +, <i>pyogenes</i> | | + |
| <i>Chlamydia</i> | - | | | | | + |
| <i>Trypanosome brucei</i> <i>rhodesiense</i> | - | | + | | | |
| <i>Coxiella burnetii</i> (riccacia, Q fever) | + | | | + | + | |
| <i>Porphyromonas gingivalis</i> | - | | + | | | |
| <i>Helicobacter pylori</i> | + | | + | +2 | | |
| <i>Haemophilus influenzae</i> | - | | + | | + | +3 |

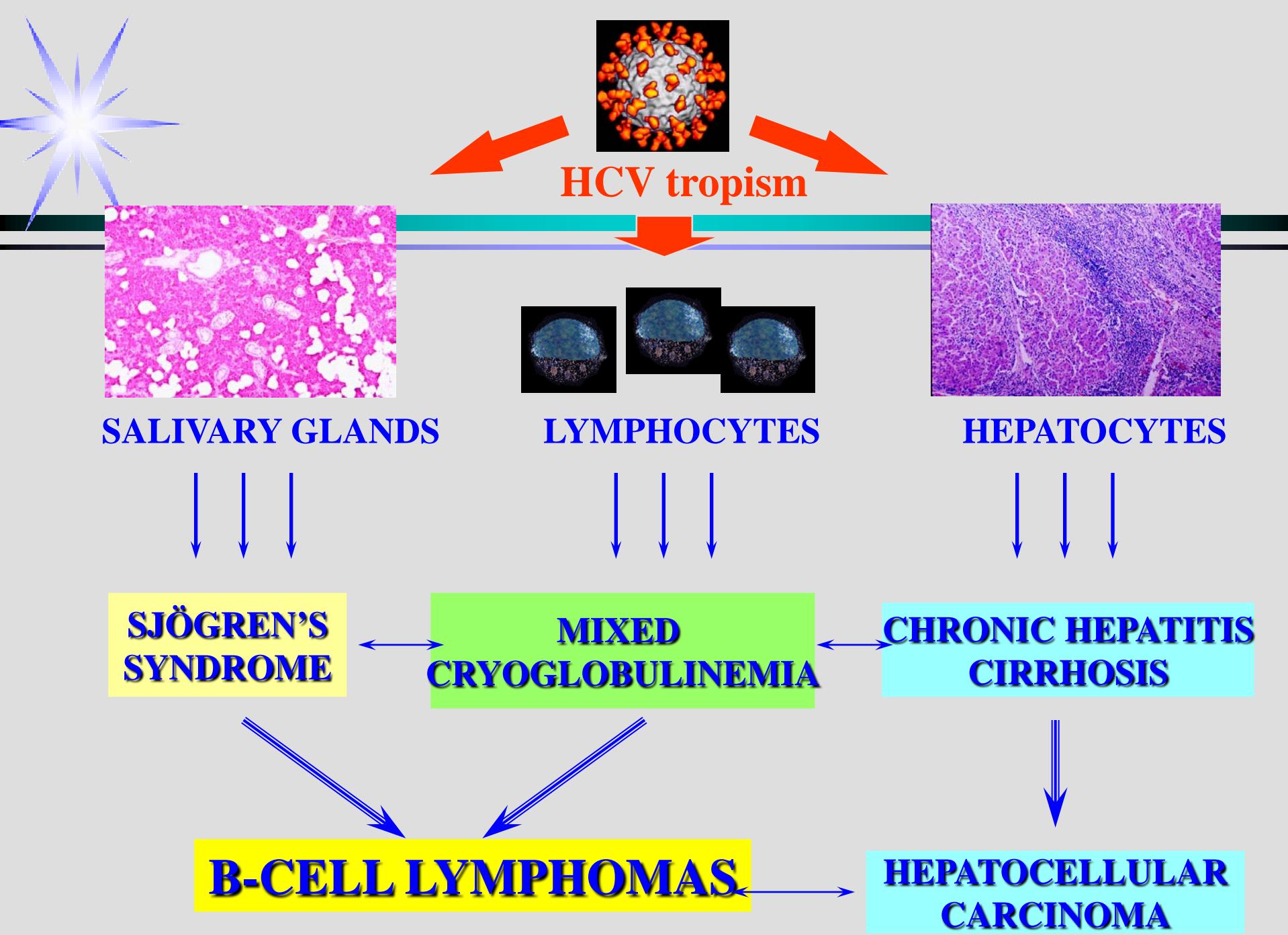


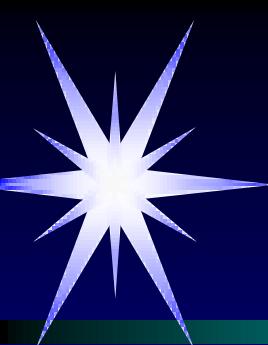
EULAR PRIZE 2005
Yehuda Shoenfeld
Pier Luigi Meroni
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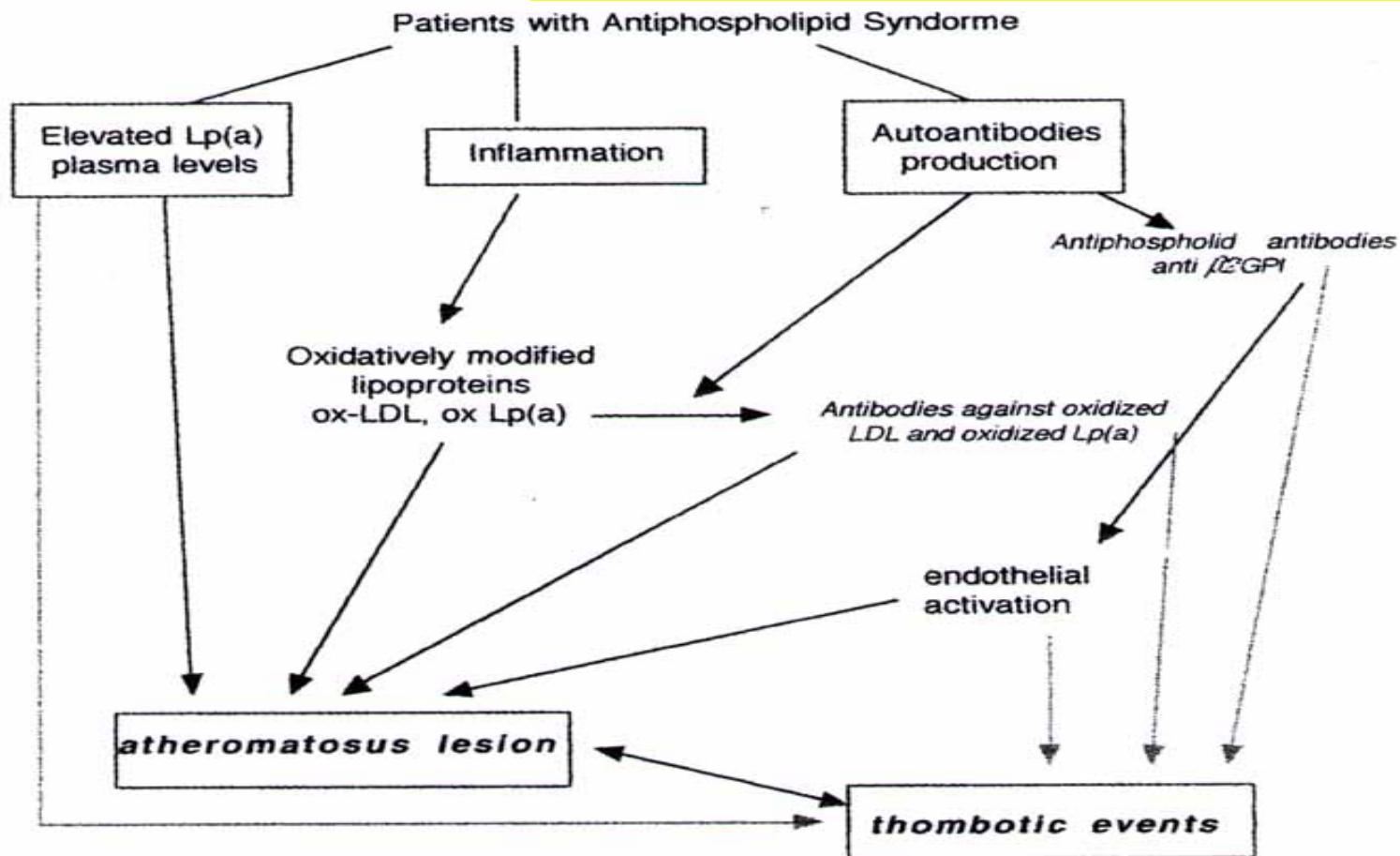
AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

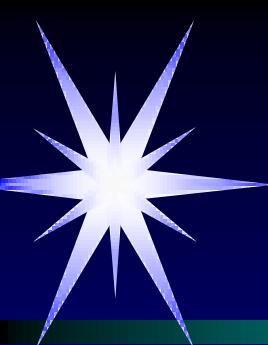
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- ↗ 7. Cancer and AID
- ↗ 8. Atheromatosis and AID
- ↗ 9.
- ↗ 10.

Antiphospholipid Syndrome and Atherosclerosis

Olga Amengual¹, Tatsuya Atsumi², Munther A. Khamashta¹ and Graham R.V. Hughes¹

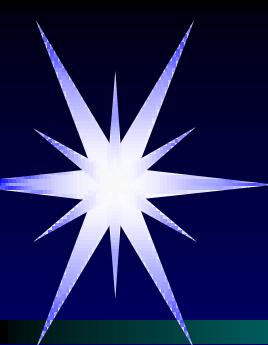
¹Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, London, United Kingdom; ²Department of Medicine II, Hokkaido University School of Medicine, Sapporo, Japan





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- ↗ 7. Cancer and AID
- ↗ 8. Atheromatosis and AID
- ↗ 9. Psychiatry and AID
- ↗ 10.



REVIEWS OF THERAPEUTICS

The Case for Autoimmunity in the Etiology of Schizophrenia

Carroll-Ann W. Goldsmith, D.Sc., and Donald P. Rogers, Pharm.D.

The treatment of schizophrenia has frustrated clinicians for over 50 years. Despite advances in neurotransmitter identification and the development of drugs targeting these transmitters, total remission of the disease is not always achieved. Potential etiologies other than neurotransmitter dysfunction merit consideration. One intriguing concept is the possible contribution of autoimmunity in patients with the disease. This breakdown of self-tolerance has been implicated in patients with other chronic diseases, such as type 1 diabetes mellitus and myasthenia gravis. The literature on autoimmunity as a possible mechanism in the pathogenesis of schizophrenia can be conflicting, but there is a substantial amount of circumstantial, although not conclusive, evidence of immune dysfunction in patients with schizophrenia.

Key Words: schizophrenia, autoimmunity, autoantibodies, immunosuppressants, etiology, immunosuppressive therapy.
(Pharmacotherapy 2008;28(6):730-741)

Table 1. Systemic Autoantibodies Associated with Schizophrenia

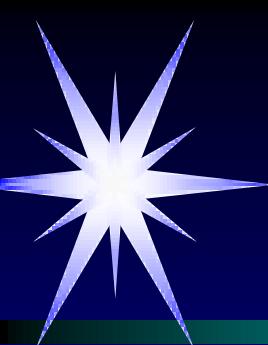
| Antibody | Antibody Titers in Patients with Schizophrenia Compared with Controls |
|--|--|
| ANA (includes several nuclear antigens) ^b | Increased ^{17-24, a} |
| ANA | No significant difference ²⁵ |
| Anticardiolipin | Increased ^{26, a} |
| Anti-PAM | Increased ^{27, a} |
| Anti-HSP 60 | Increased ^{27-29, a} |
| Anti-HSP 60 | No significant difference ³⁰ |
| Anti-HSP 70 | Increased ^{29, 31, a} |
| Anti-HSP 90 | Increased ^{31, a} |
| Autoantibody panel ^c | Increased ^a in left-handed but not right-handed patients ^{22, 23} |
| Rheumatoid factor | No significant difference ²⁵ |
| Anti-leukocyte elastase | Increased ^a in patients with negative but not positive symptoms ³² |
| Platelet-associated inhibitor of dopamine binding | Increased ^a but not correlated with disease severity ^{33, 34} |
| Antigluten | Increased ^{35, a} |
| Antigliaden | Increased ^{35, a} |
| Anti-β-lactoglobulin | Increased ^{35, a} |
| Anticasein | Increased ^{35, a} |

Table 2. Organ-Specific Autoantibodies Associated with Schizophrenia

| Antibody | Antibody Titers in Patients with Schizophrenia Compared with Controls |
|------------------------|--|
| Antibrain ^b | Increased ^{36, a} |
| Antiserotonin | Increased ^{37, a} |
| Antidopamine | No significant difference ¹⁸ |
| Anti-HTR _{1A} | No significant difference ³⁸ |
| Anti-CHRM ₁ | Increased ^{38, a} |
| Anti-OPRM ₁ | Increased ^{38, a} |
| Anti-DRD ₂ | No significant difference ^{38, 39} |
| Anti-nAChR | Increased ^{40, a} |
| Anti-mAChR | Increased ^{41, 42, a} |
| Anti-NGF | Increased ^a in patients with positive but not negative symptoms ³² |
| Antiganglioside | No significant difference ⁴³ |

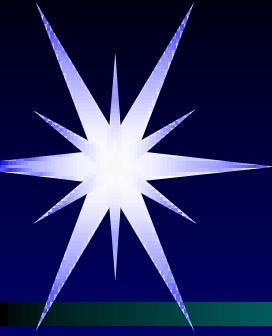


11. 4. 2000



AUTOIMMUNE DISEASES: CHALLENGES FOR THE 21th CENTURY

- ↗ 1. Great variety of conditions
- ↗ 2. Polysymptomatic/Multidisciplinary
- ↗ 3. Worldwide distribution
- ↗ 4. Two Stars: SLE & APS
- ↗ 5. One Challenge: Systemic sclerosis
- ↗ 6. Infections and AID
- ↗ 7. Cancer and AID
- ↗ 8. Atheromatosis and AID
- ↗ 9. Psychiatry and AID
- ↗ 10. Laboratory diagnosis



ANA

ds-DNA

SS-A/Ro

SS-B/La

RNP

Sm

RF

LA

Scl-70

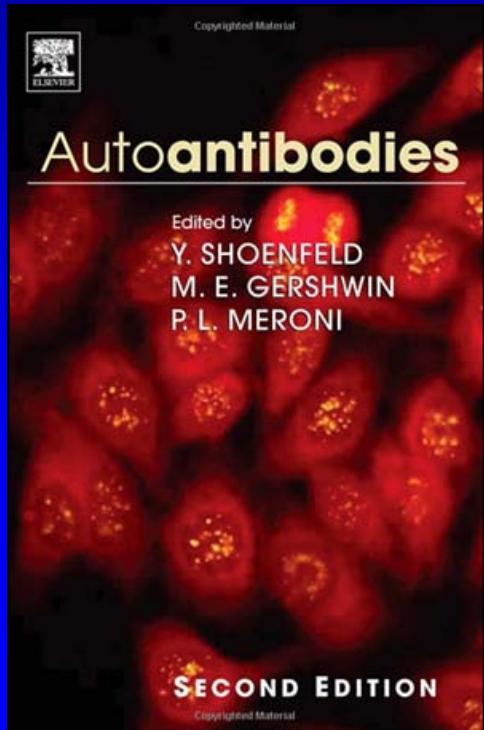
p-ANCA

aCL

c-ANCA

a- β_2 GPI

Anticentromer





APS

PM

DM

SLE

SSc

MS

SS

CAPS

DM

WG

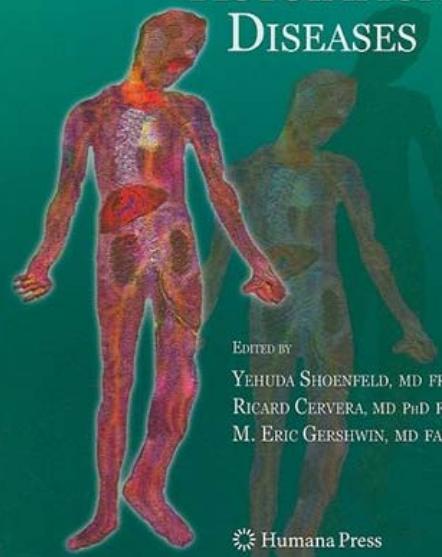
MCTD

IBD

PAN

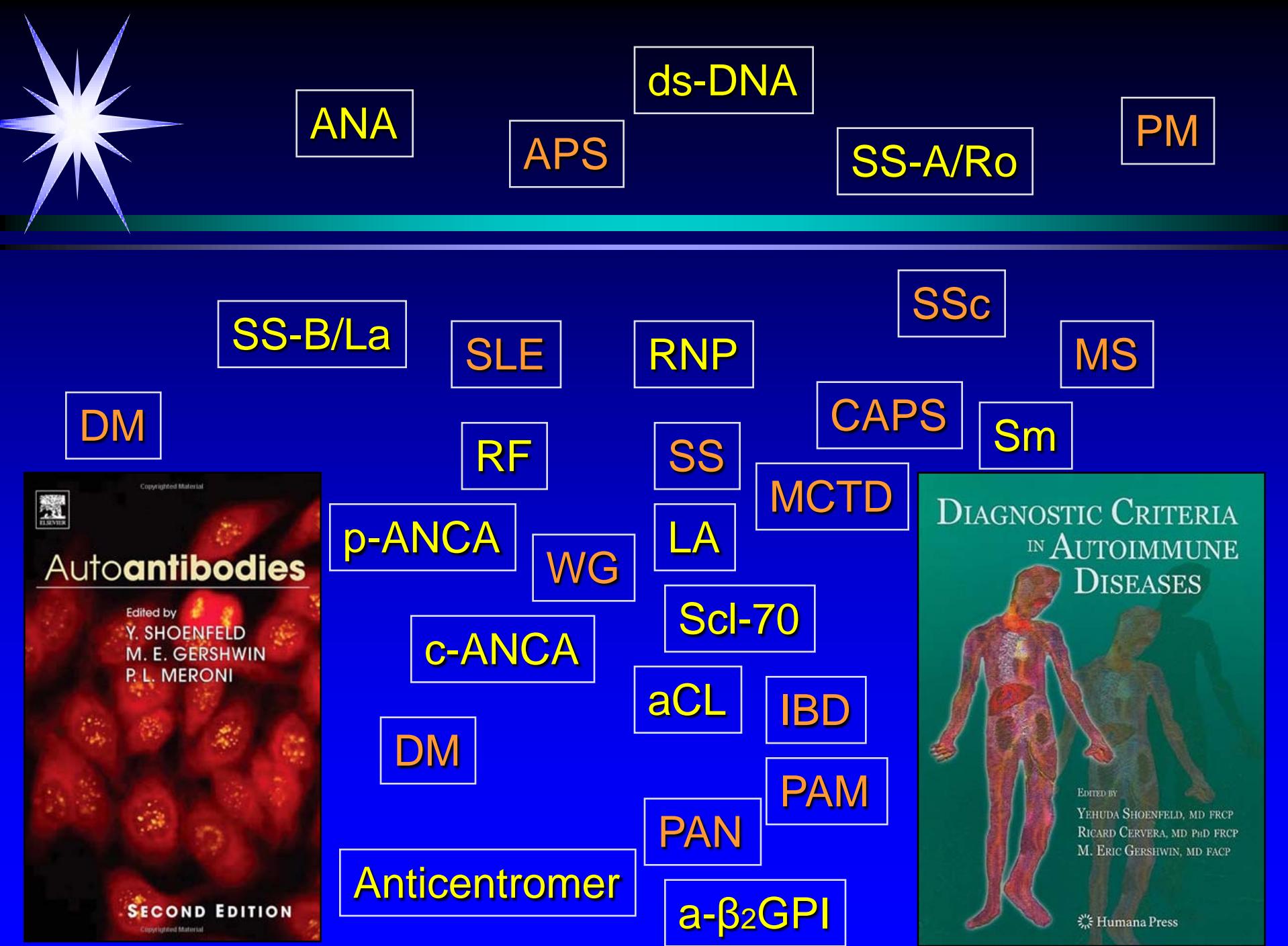
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DIAGNOSTIC CRITERIA
IN AUTOIMMUNE
DISEASES



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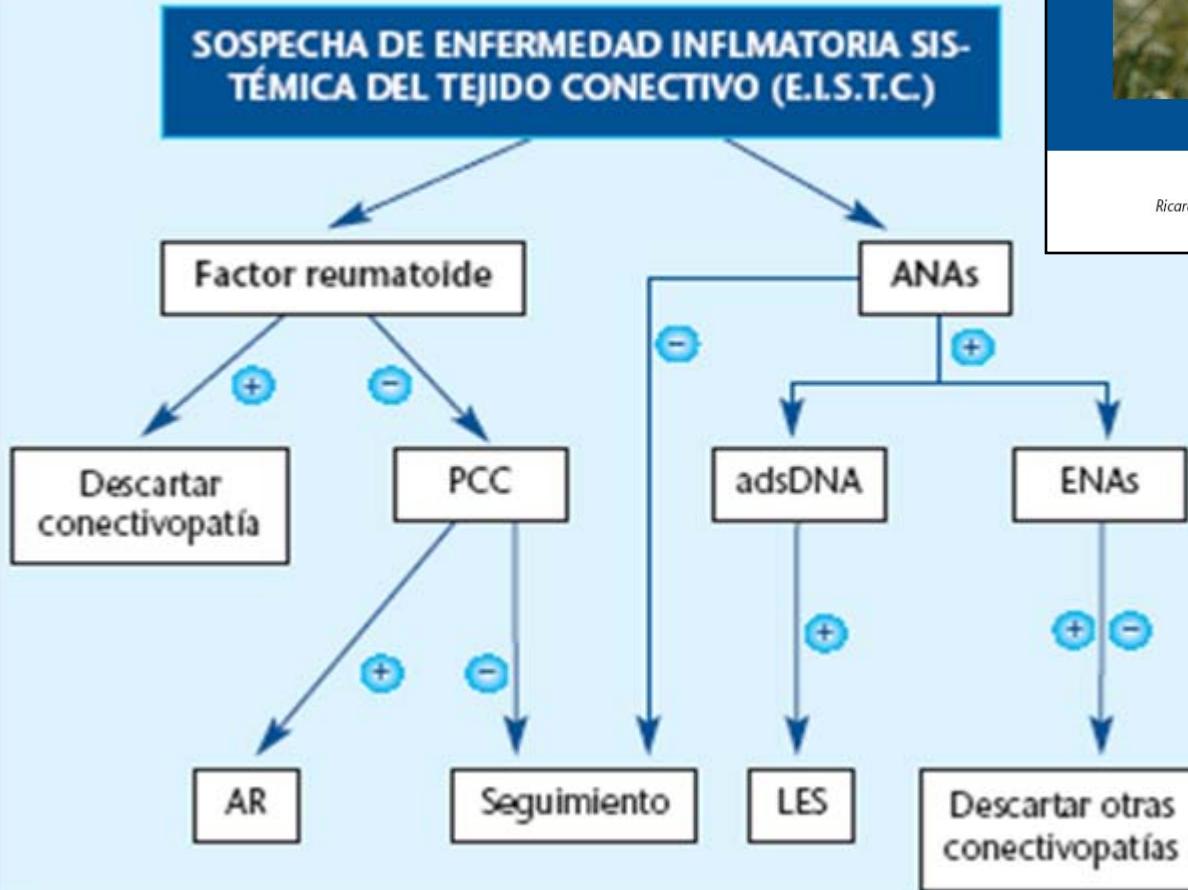
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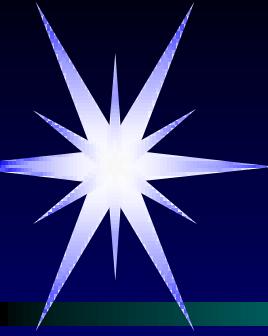
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ANA Testing – A Hot Issue

*May 8th, 2010, 14:00 – 16:00 h (Hall B)
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