Infection, Genetics and Autoimmunity – a Mosaic

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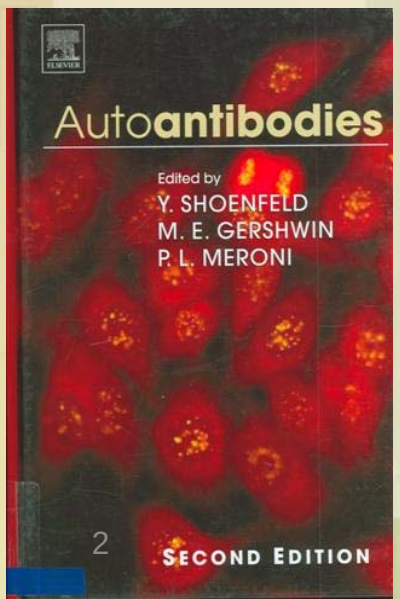
Stiges 23 11 07

Israel

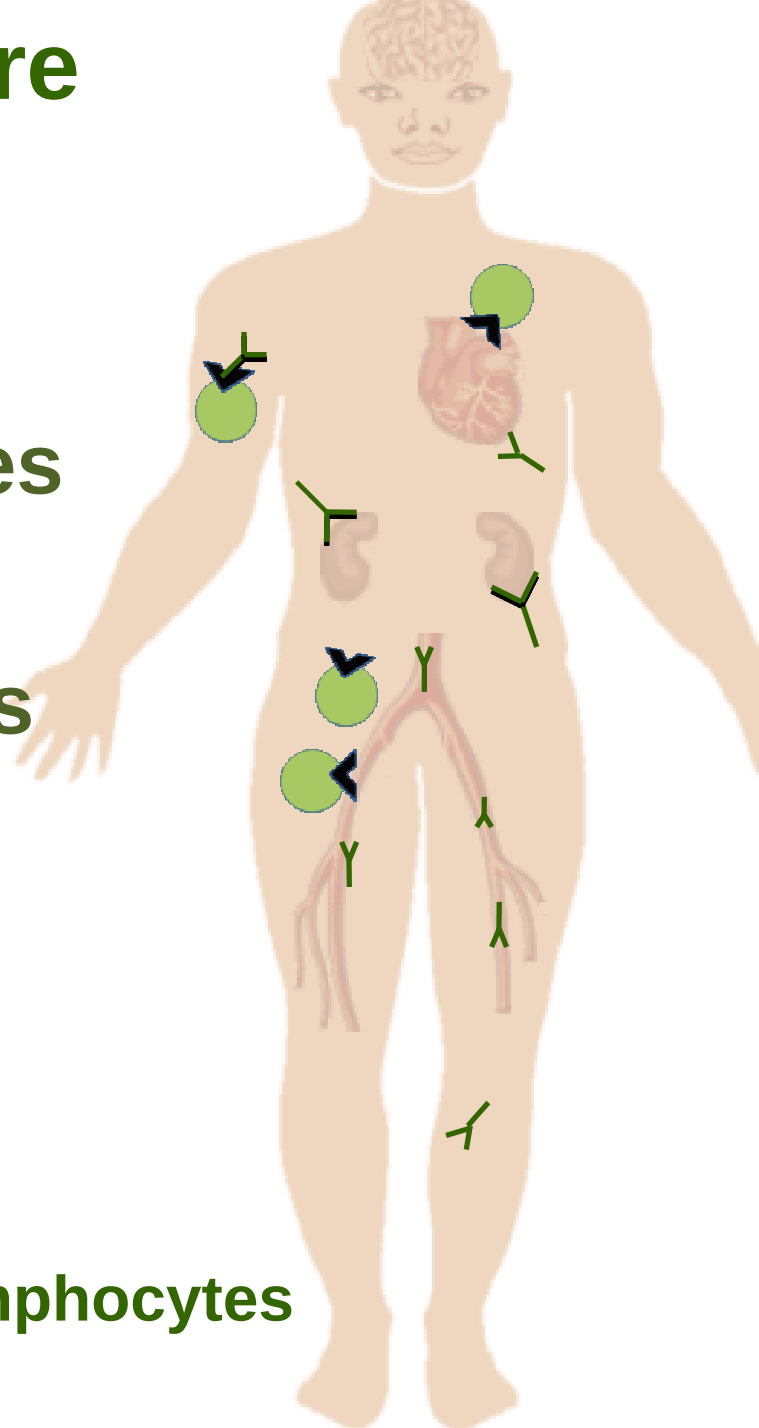
Autoimmune diseases are characterized by the presence of:

- Auto-reactive lymphocytes in affected tissue
- Circulating autoantibodies



Autoantibody

Auto-reactive lymphocytes



Autoimmunity

1) Why does Ms. X develop SLE at the age of 30?

2) Why does Mr. Y present with Goodpasture's Syndrome at the age of 50?

   a) Why him and her?

   b) Why the specific disease?

   c) Why at that specific time?

The major pieces of the mosaic of autoimmunity

Genetics:

- Increased incidence of the disease in families.
- Increased incidence of autoantibodies in first-degree relatives of a patient.
- Increased incidence of the disease in monozygotic twins.
- HLA studies – increased incidence of HLA-B8, DR2, DR3, DR4 in some diseases. A protective effect, e.g. HLA DR2 in type 1 diabetes.

The major pieces of the Mosaic of Autoimmunity

Defects in immune system:

- IgA deficiency.
- Complement component deficiencies (e.g.C1q, C2, C4).
- Qualitative and quantitative defects in T suppressors (CD4+25+) (Treg).
- Defects in natural killer (NK) cells.
- Defects in apoptosis (Fas) or phagocytosis.

The major pieces of the Mosaic of Autoimmunity

Sex and autoimmunity

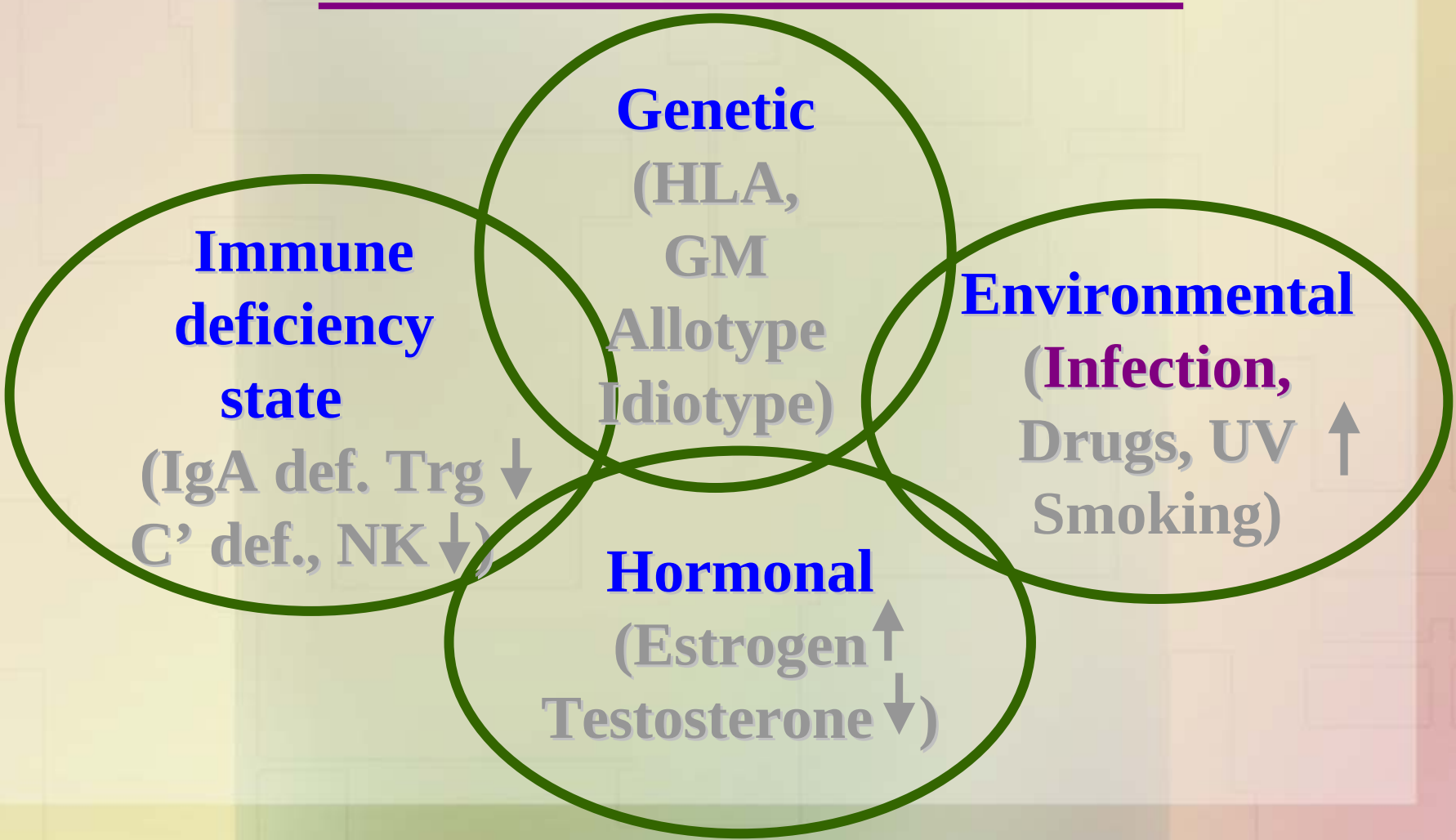
- Females have, on the average, higher Ig levels than males.
- Females have an enhanced antibody production to both primary and secondary Ag stimulation.
- Females have a higher CMI response (e.g. homograft rejection).
- Males are more prone to infections .
- In male animals, it is easier to produce immune tolerance.

The major pieces of the Mosaic of Autoimmunity

Environmental:

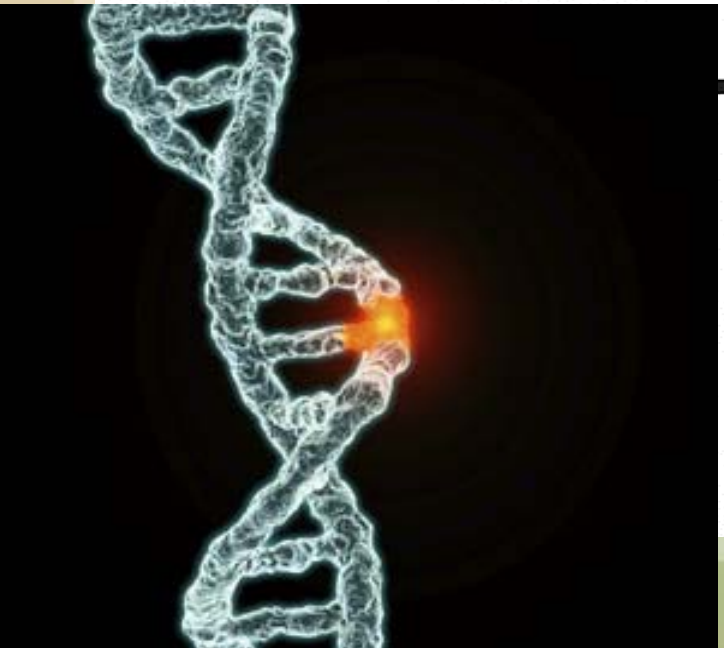
- **Infecting agents**: viruses, bacteria, parasites.
- Drugs (e.g. idiopathic thrombocytopenia purpura, myasthenia, SLE).
- Toxins (e.g. scleroderma).
- Cosmetics (e.g. silicone).
- UV light (e.g. SLE).
- Smoking (e.g. Goodpasture's syndrome,RA,Thyr).
- Stress (e.g. SLE)
- Nutritional influence (e.g. RA, SLE).

The mosaic of autoimmunity



Environmental Factor

Genetic susceptible individual



Autoimmune Disease

Some might say:

- **“Everything is autoimmune until proven otherwise”**

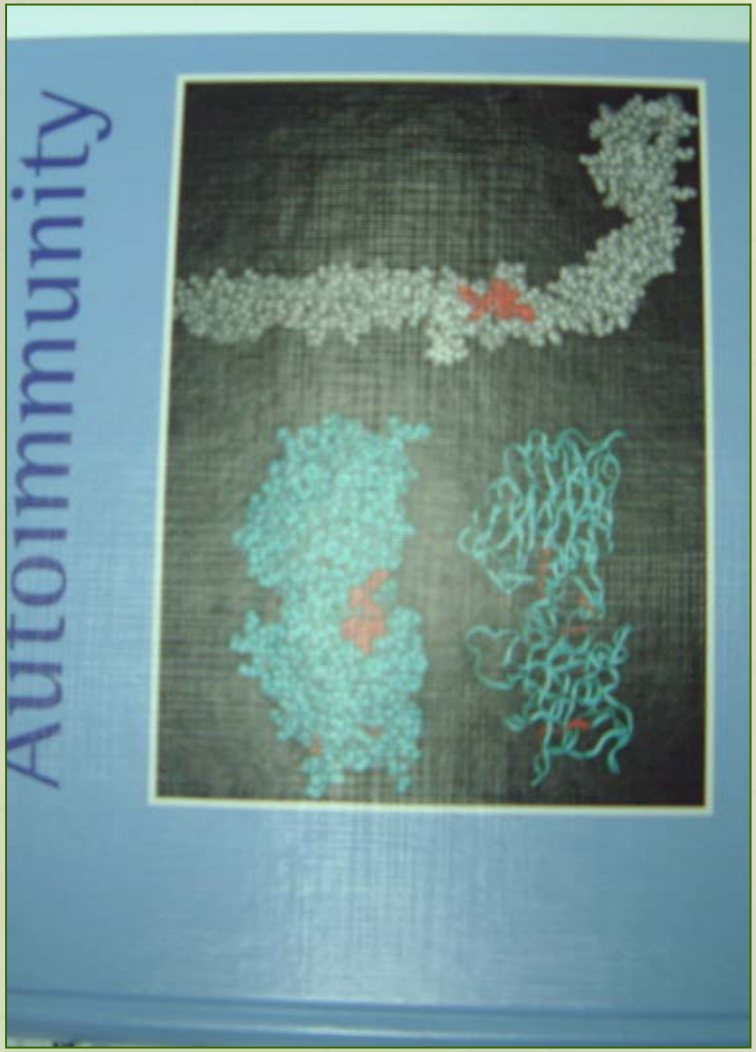
Others will claim:

- **“Everything is infectious until proven otherwise”**

Others insist:

- **“Everything is genetic until proven otherwise”**

Infection and Autoimmunity



Rheumatic Fever

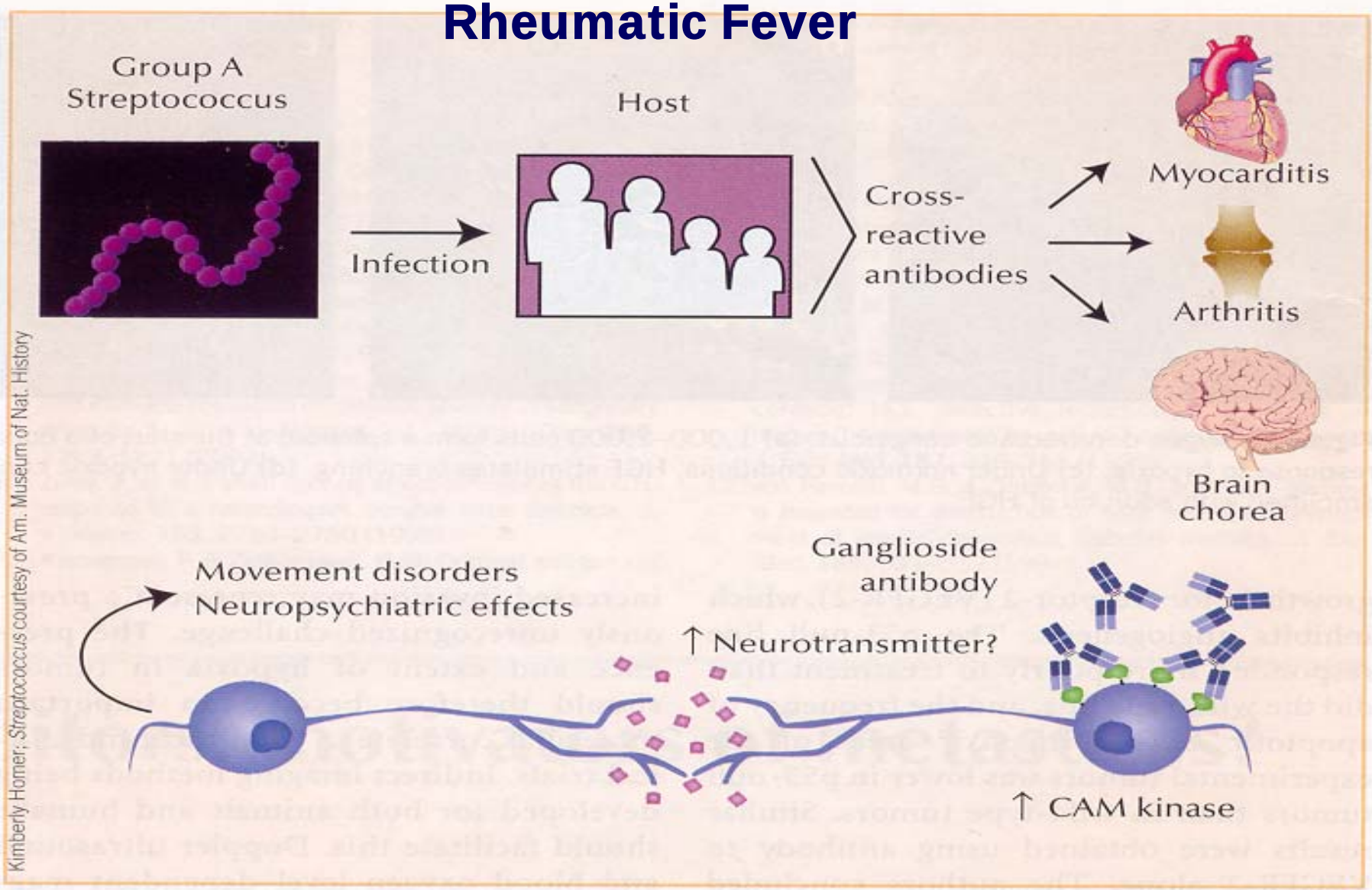


Figure 1 Autoantibodies and Sydenham chorea. The pathology of this disease could result from an antibody against a streptococcal surface carbohydrate that cross-reacts with a glycolipid molecule on neurons in the basal ganglia. Autoantibody binding of the glycolipid activates calcium/calmodulin-dependent protein (CaM) kinase in neuronal cells, thus potentially affecting neurotransmitter release or other cell functions that could result in the aberrant behaviors seen in Sydenham chorea.

Rheumatic fever: from sore throat to autoimmune heart lesions.

Guilherme L, Kalil J.

Int Arch Allergy Immunol. 2004;134:56-64.

- **HLA-DR7DR53 associated with DQ molecules seem to be related with the development of valvular lesions in severe RHD patients.**
- **DR7DR53 molecules were also involved in the recognition of an immunodominant M5 peptide in these patients.**

Mechanisms for induction of autoreactive T and B cells by infectious agents:

Molecular mimicry

T/B cell activation by microbial peptides that share sufficient similarity to self peptides

Viral and bacterial superantigens

Activation of autoreactive T cells that express particular Vβ segments

Enhanced presentation & processing of autoantigen

Priming of autoreactive lymphocytes leading to “epitope spread”.

Bystander activation

Expansion of previously activated T cells at an inflammatory site

Activation of lymphocytes by lymphotropic viruses

- Wucherpfennig KW, Mechanisms for the induction of autoimmunity by infectious agents, J Clin Invest. 2001

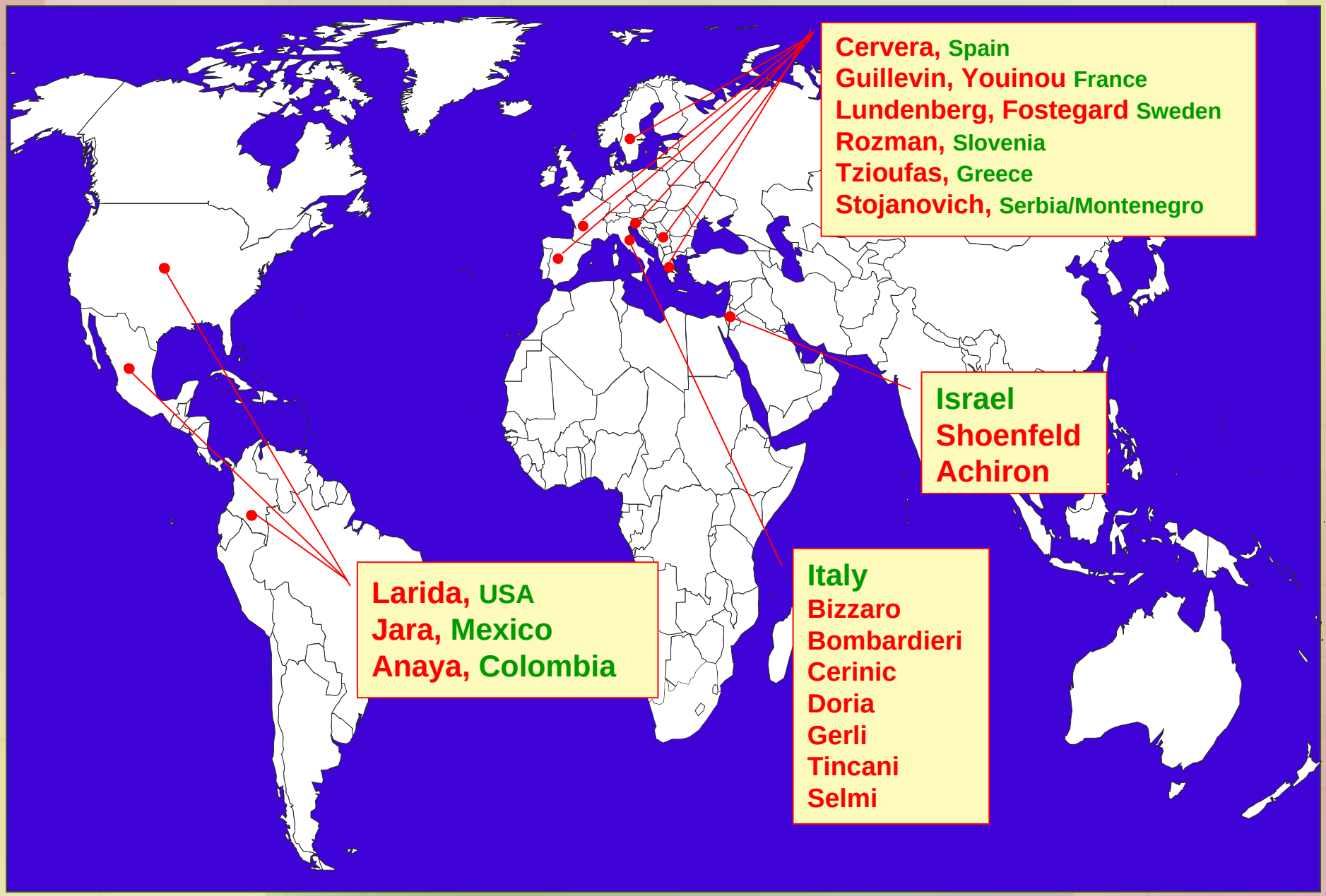
Most consistent associations between infecting agents and autoimmune disease

1. **Epstein Barr Virus** (MS, SLE, RA, Sjögren's syndrome)
2. **Cytomegalovirus** (SLE, Atherosclerosis, Diabetes mellitus, Systemic sclerosis, IBD)
3. **Helicobacter pylori** (ITP, SSc, Crohn's disease, GBS,AS)
4. Chlamydia pneumoniae (Atherosclerosis, MS)
5. Parvovirus B19 (SSc?)
6. E. coli (RA)
7. P. mirabilis (RA)
8. Yersinia enterocolitica (IBD,)
9. C.jejuni (GBS)

Study Outline

- Over 4,000 serum samples of a wide variety of autoimmune diseases were gathered from all around the world.
- Patient clinical data including sex, age and clinical manifestations were obtained.
- Over 800 samples also have genetic HLA imprints.
- Phase 1 – a total of 1,670 serum samples were screened for various antibodies.

World-wide Collaboration



Phase 1 sample population included:

- **120** Systemic lupus erythematosus
- **152** Rheumatoid arthritis
- **98** Anti-phospholipid syndrome
- **99** Multiple sclerosis
- **82** Sjogren syndrome
- **69** Primary biliary cirrhosis
- **63** SLE+APS
- **101** Polymyositis
- **80** Systemic sclerosis
- **119** IBD (80 Crhon's, 39 ulcerative collitis)
- **90** Diabetes mellitus
- **29** Pemphigus vulgaris
- **50** Hashimoto thyroiditis
- **70** Graves' disease
- **5** Hyperthyroidism
- **41** Mixed cryoglobulinemia
- **35** Giant cell arthritis
- **20** Cryoglobulinemia
- **10** Wegener's granulomatosis
- **9** Microscopic polyangitis
- **6** Churg strauss
- **7** Polyarteritis nodosa
- **140** Control (Columbia)
- **100** Control (Italy)

Total:

- **1670** samples
- **23** disease groups

Methods

- All samples were processed using two methods:
  - **BioPlex 2200 multiplex diagnostic platform (Bio-Rad)**:

    A fully automated, random-access system built on a synthesis of multiplexed suspension array, magnetic bead and flow cytometry technologies.
  - **ELISA**

Serologic testing included:

- **ANA Screen Kit**
  - SSA (60 & 52kD)
  - SSB
  - Sm
  - SmRNP
  - RNP (A & 68kD)
  - dsDNA
  - Chromatin
  - Scl-70
  - Ribosomal-P
  - Jo-1
  - Centromere-B

- **Vasculitis Kit**
  - GBM (glomerular basement membrane)
  - PR3 (proteinase 3)
  - MPO (myeloperoxidase)

- **Gastrointestinal Kits (IgG and IgA)**
  - ASCA
  - Gliadin
  - tTg

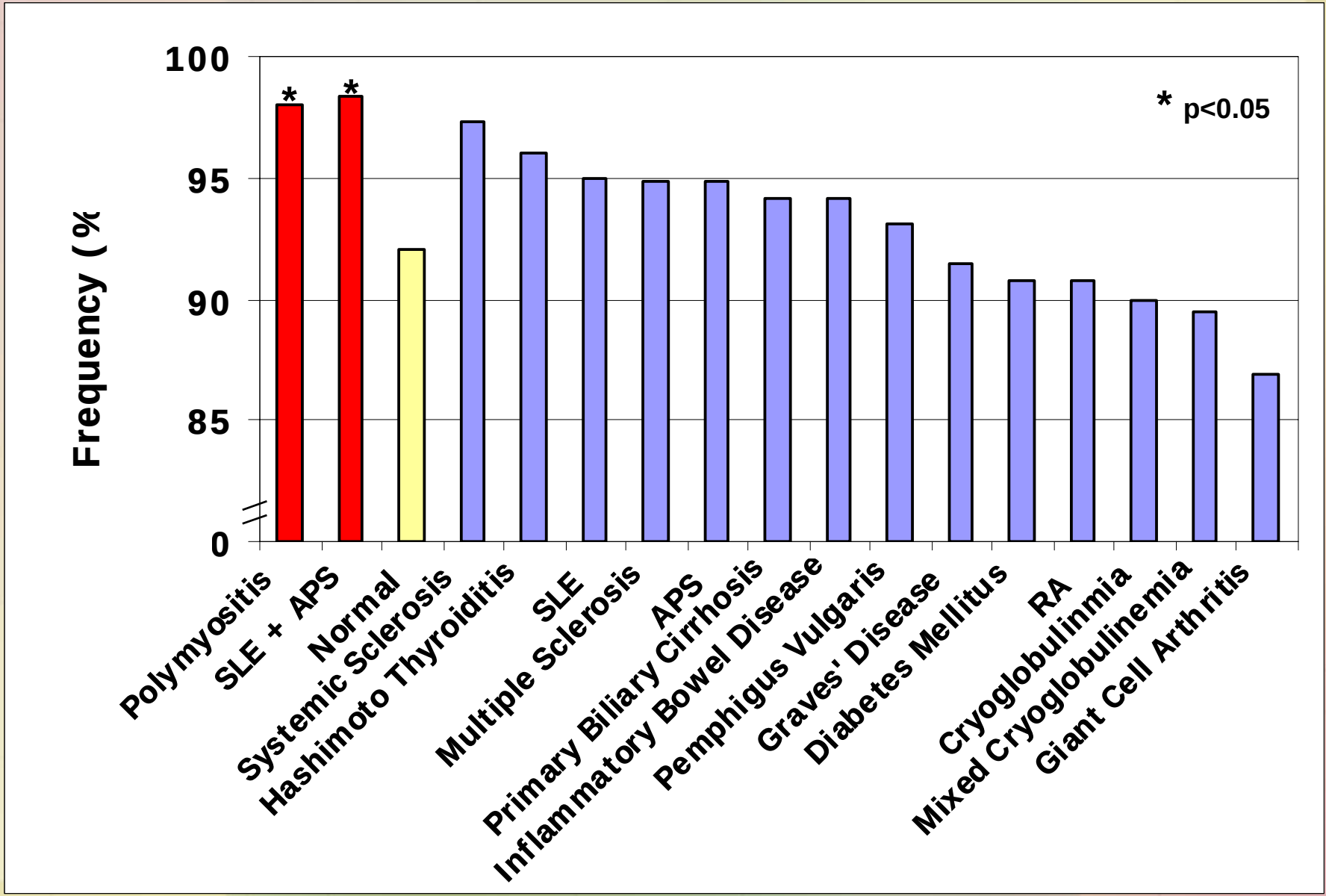
- **Antiphospholipid syndrome Kits (IgG and IgM)**
  - B2GP1
  - Cardiolipin
  - PS (phosphatidylserine)
  - PT (prothrombin)

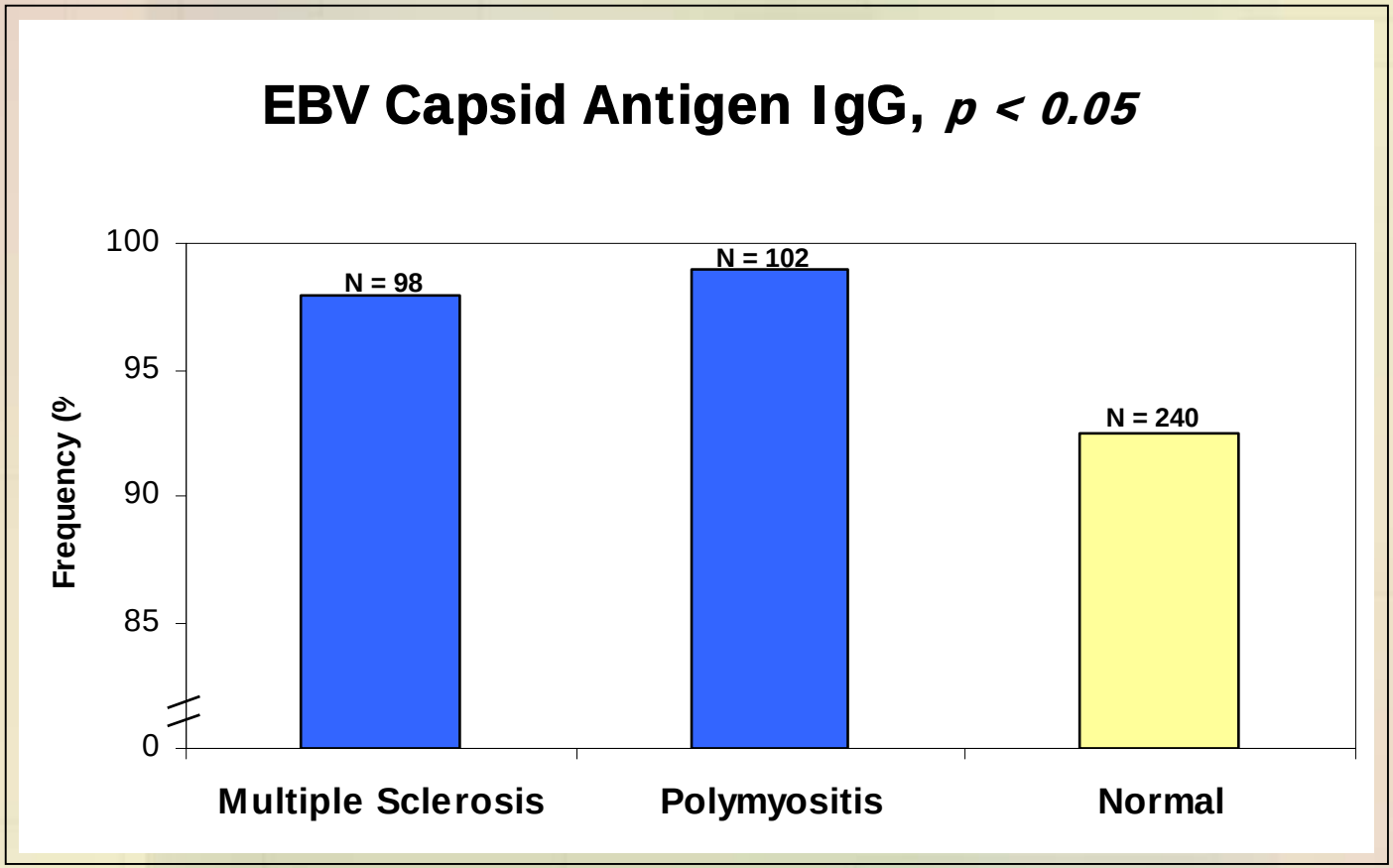
Epstein-Barr Virus

- Large body of evidence indicating that EBV infection has a major role in pathogenesis of organ-specific and non-organ-specific chronic autoimmune diseases.
- Firmly established relationship with multiple autoimmune disease i.e.; **SLE**, **MS**, **RA**, **Sjogren's syndrome**, **autoimmune thyroid disease**, **systemic sclerosis**, **autoimmune liver disease** and **IBD**.

- Poole BD et al, Epstein-Barr virus and molecular mimicry in systemic lupus erythematosus. *Autoimmunity*. 2006
- Pender MP, Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases., *Trends Immunol, 2003*

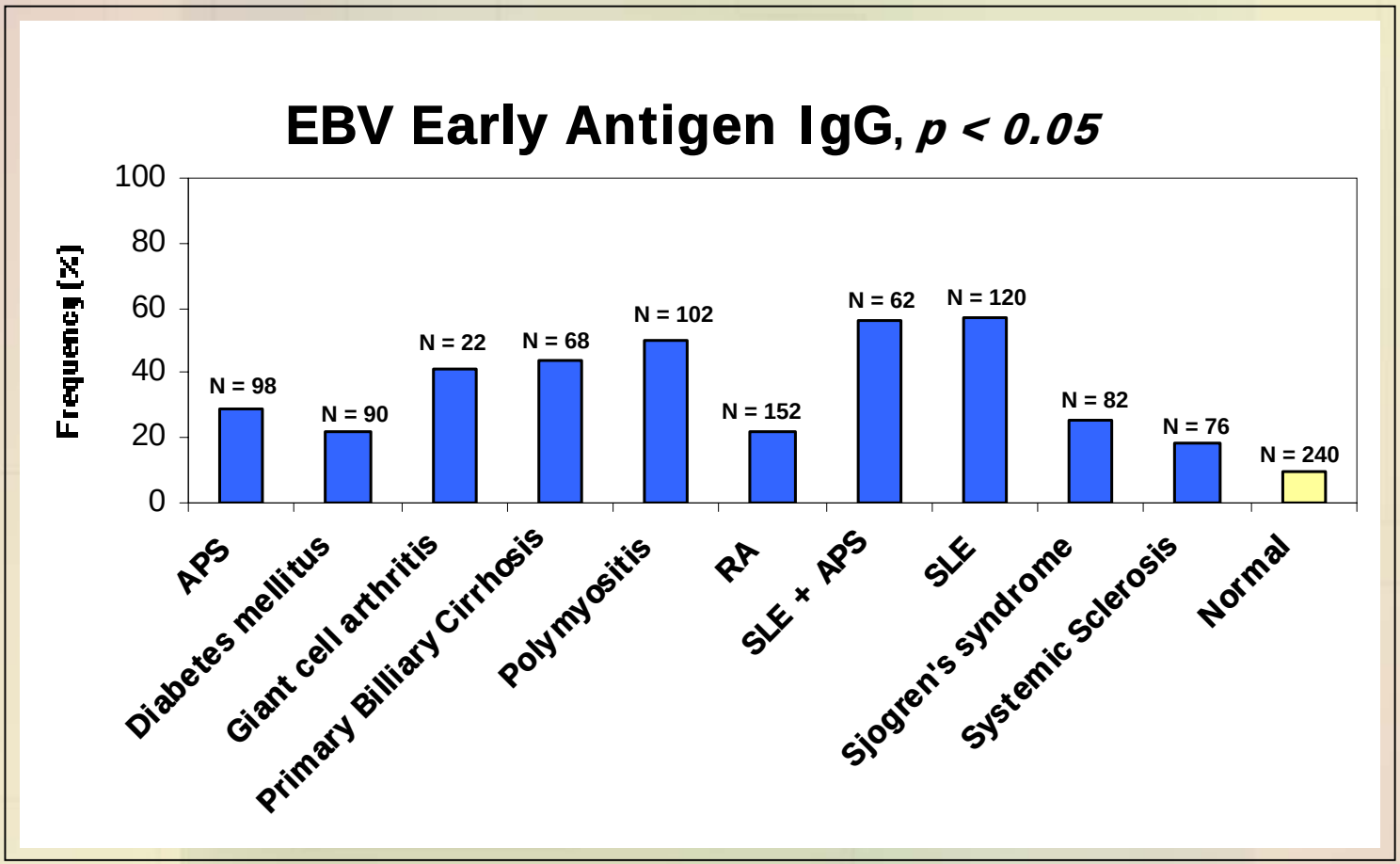
EBV Nuclear Antigen (EBNA) IgG





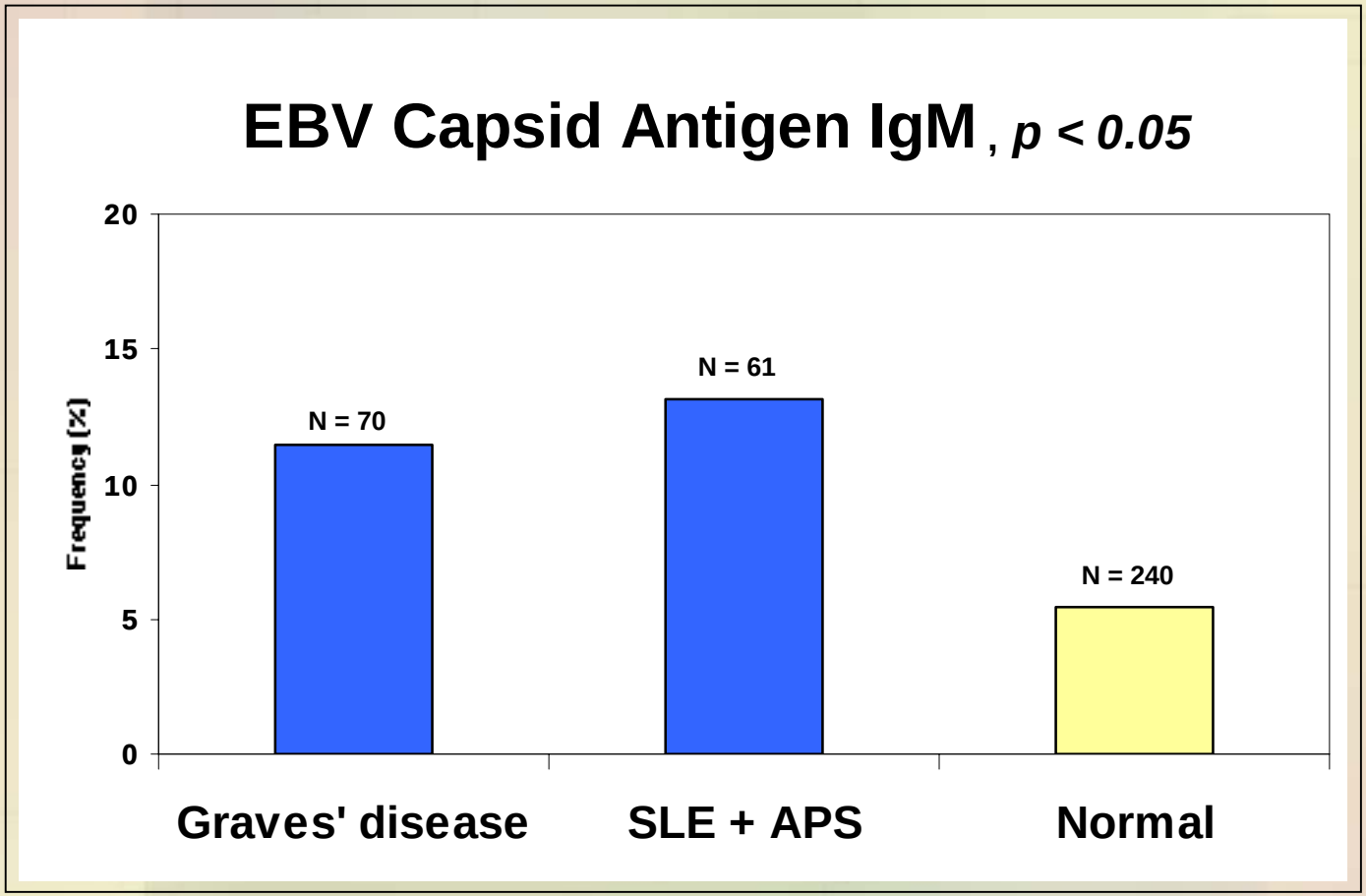
P > 0.05

RA, SLE, APS, SLE+APS, Diabetes, Sjogren's syn, Systemic sclerosis, IBD, Graves', Hashimoto, Cryoglobulinemia, Pemphigus, Giant cell arthritis



P > 0.05

MS, IBD, Graves', Hashimoto, Cryoglobulinemia, Mixed Cryoglobulinemia, Pemphigus Vulgaris



P > 0.05

RA, MS, SLE, APS, Diabetes, Sjogren's syn, Systemic sclerosis, IBD, Graves', Hashimoto, Cryoglobulinemia, Polymyositis, Pemphigus, Giant cell arthritis

Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases.

Pender MP. Trends Immunol. 2003;24:584-8.

- There is now a large body of evidence implicating the virus in several different autoimmune diseases, including:

SLE, multiple sclerosis, Sjogren's syndrome, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, cryptogenic fibrosing alveolitis and pure red cell aplasia.

Expression of the Epstein-Barr virus nuclear antigen-1 (EBNA-1) in the mouse can elicit the production of anti-dsDNA and anti-Sm antibodies.

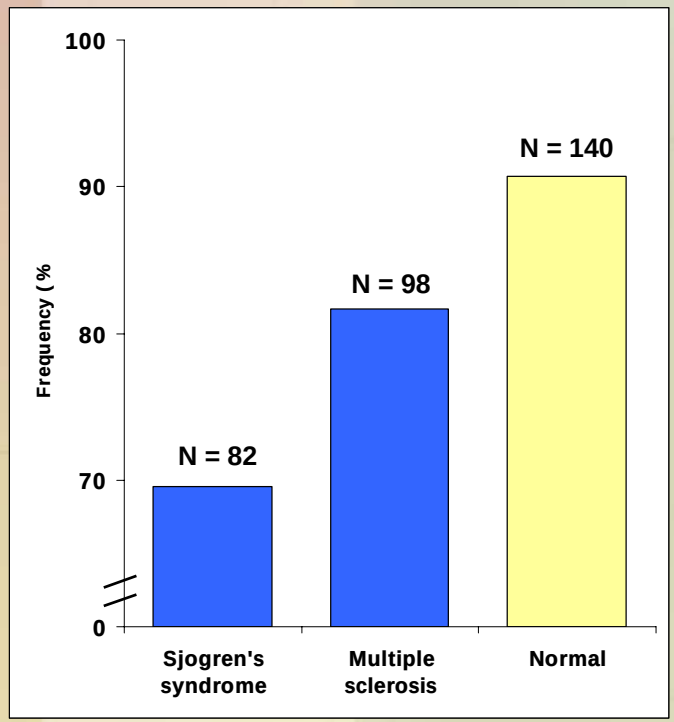
Sundar K, et al. J Autoimmun. 2004;23:127-40.

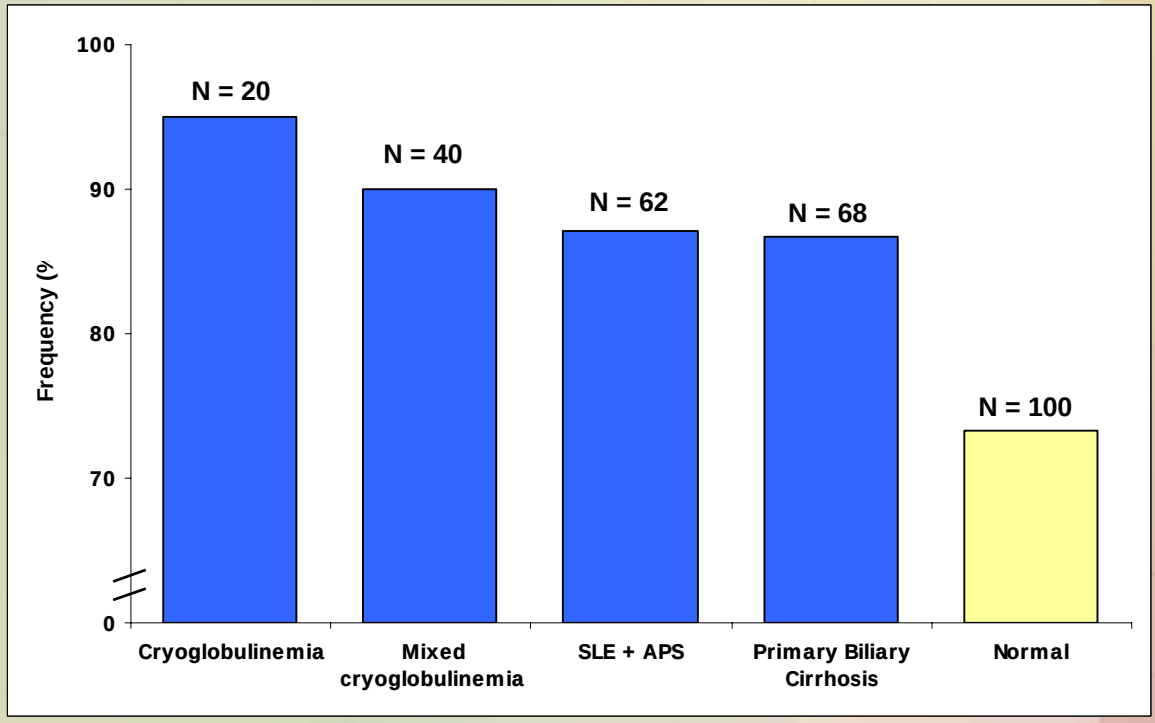
Cytomegalovirus - CMV

- Between 50% and 80% of adults in the United States are infected with CMV by 40 years of age. (CDC)
- Known association with **SLE**, **atherosclerosis**, **DM**, **IBD**, **MS** and **Systemic sclerosis**.

- Sekigawa et al, Cytomegalovirus infection in patients with systemic lupus erythematosus, Clin Exp Rheumatol, 2004
- Nerheim et al, Enhanced cytomegalovirus infection in atherosclerotic human blood vessels, Am J Pathol, 2004
- Roberts et al, Association of type 2 diabetes mellitus and seroprevalence for cytomegalovirus, South Med J, 2005
- Criscuoli et al, Cytomegalovirus and inflammatory bowel disease: is there a link?, World J Gastroenterol, 2006
- Guiducci et al, Infection and Systemic Sclerosis, Infection and Autoimmunity, 1st Ed., 2001

CMV IgG, *p < 0.05*





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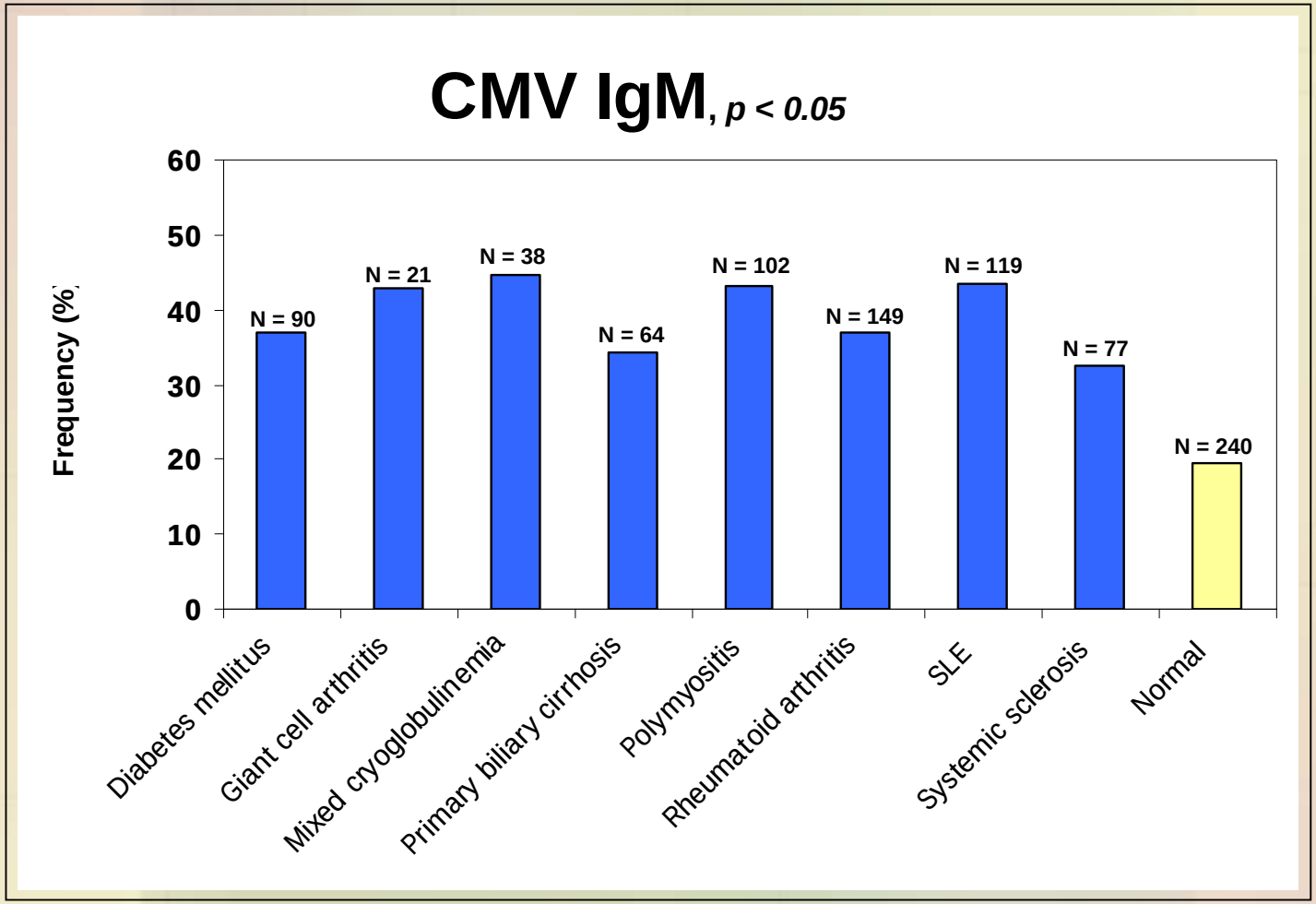
RA, SLE, APS, Diabetes, Systemic sclerosis, IBD, Graves', Hashimoto, Polymyositis, Pemphigus, Giant cell arthritis



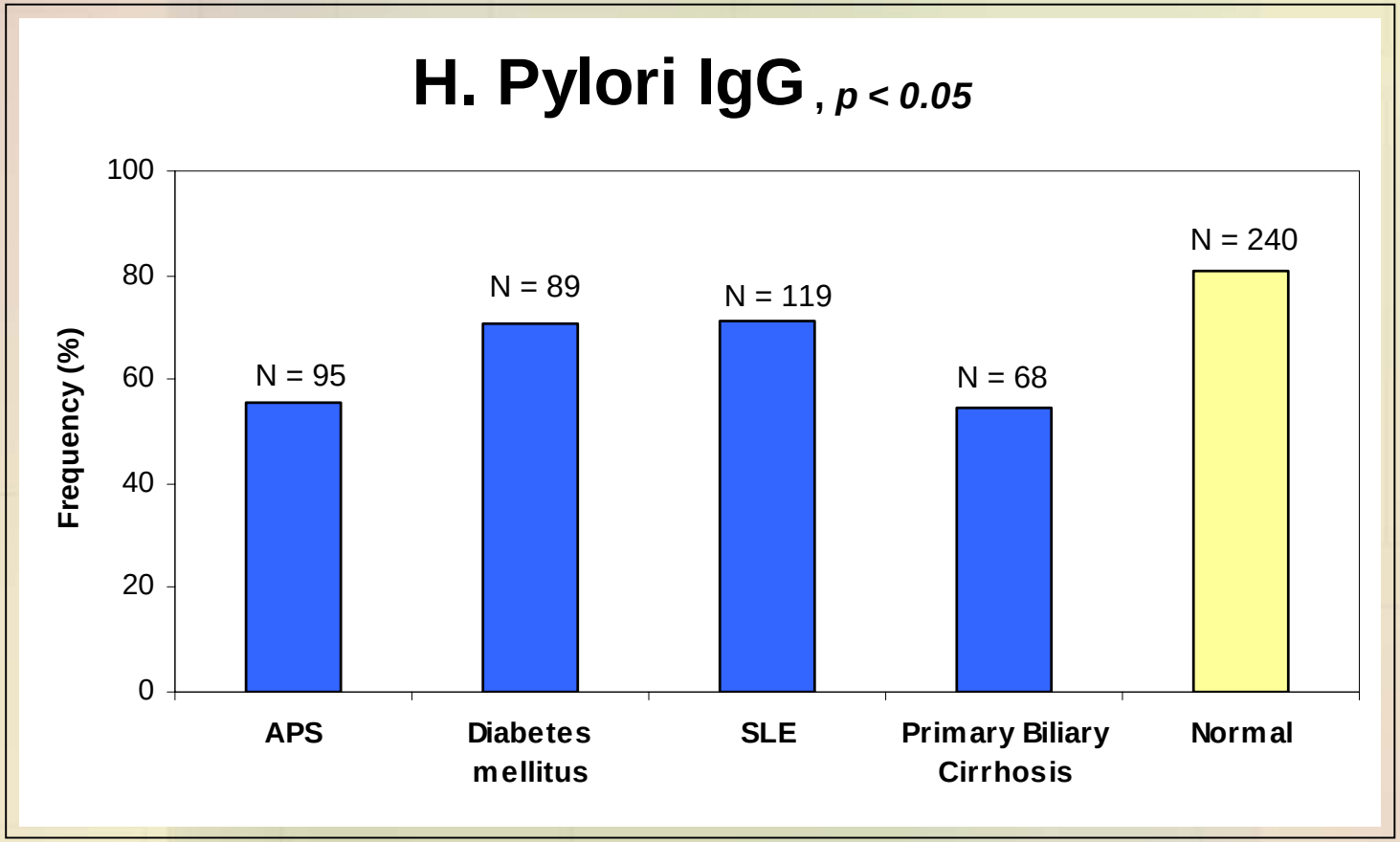
P > 0.05

MS, APS, Diabetes, Sjogren's syn, Systemic sclerosis, IBD, Graves', Hashimoto, Cryoglobulinemia, Pemphigus

Helicobacter Pylori

- Infection rates vary in different parts of the world, from 50% in the western world to 90% in Asia and the far east.
- Most remain a-symptomatic, 10-15% develop peptic ulcers, chronic gastritis, **autoimmune gastritis**, or gastric lymphoma (MALT).
- Also associated with **atherosclerosis**, **ITP**, **GBS** and **Systemic sclerosis**

- Suerbaum S. et al, Helicobacter pylori infection, N Engl J Med, 2002
- Oshima T. et al, Association of Helicobacter pylori infection with systemic inflammation and endothelial dysfunction in healthy male subjects.J Am Coll Cardiol, 2005
- Showji Y. et al, Seroprevalence of Helicobacter pylori infection in patients with connective tissue diseases.Microbiol Immunol, 1996
- Franchini M. et al, Helicobacter pylori-associated immune thrombocytopenia. Platelets , 2006



P > 0.05

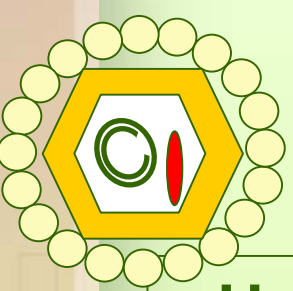
RA, MS, Sjogren's, SSc, SLE+APS, IBD, Graves', Hashimoto, Cryoglobulinemia, Polymyositis, Pemphigus, Giant cell arthritis

Conclusions

- High levels of different EBV antigens were consistently prevalent in various autoimmune diseases.
- H. Pylori was found in lower titers among patients with SLE, APS, DM and PBC when compared to controls, raising the possibility that this bacteria may play a protective role from autoimmune disease.

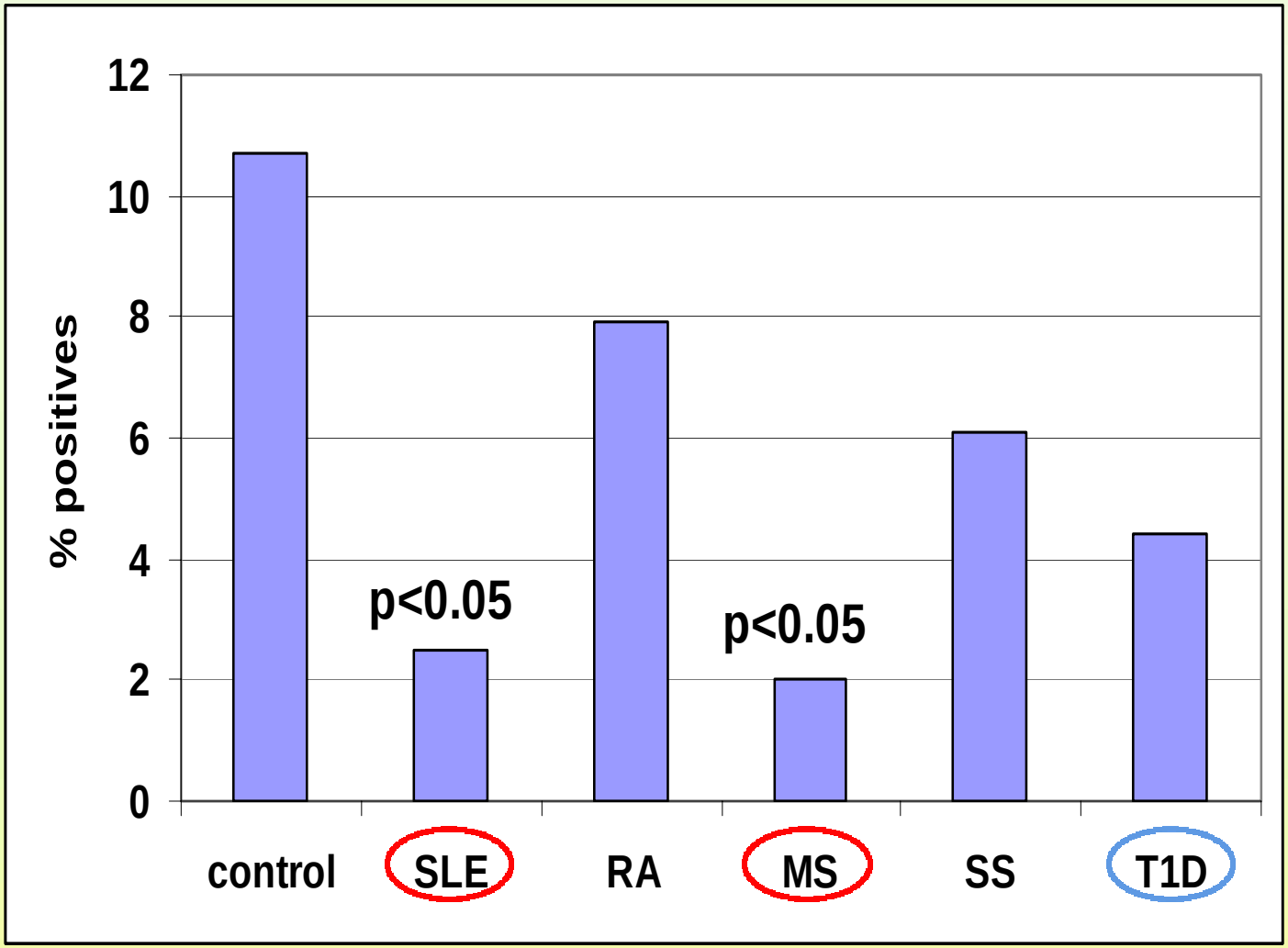
Why HBcAb?

Differentiate between people who were actually infected with HBV from those who were vaccinated



Hepatitis B virus	Hepatitis B vaccine
HBsAg → HBsAb	HBsAg → HBsAb
HBcAg → HBcAb	Adjuvant

Frequency of HBcAb



Explaining the Results

Protective role of HBV

↓

Individuals who developed SLE and MS were probably never infected with HBV

↓

Hygiene Hypothesis

Protective role of SLE

↓

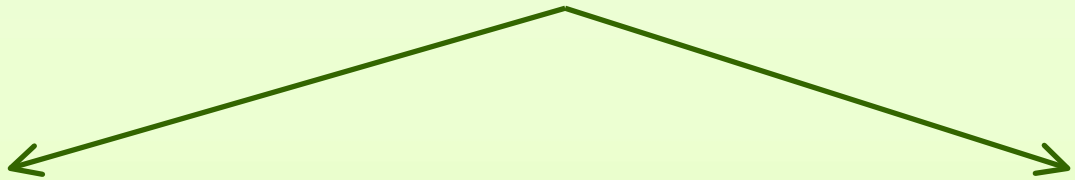
Individuals who developed SLE are protected from HBV infection

↓

INF-α

In Summary:

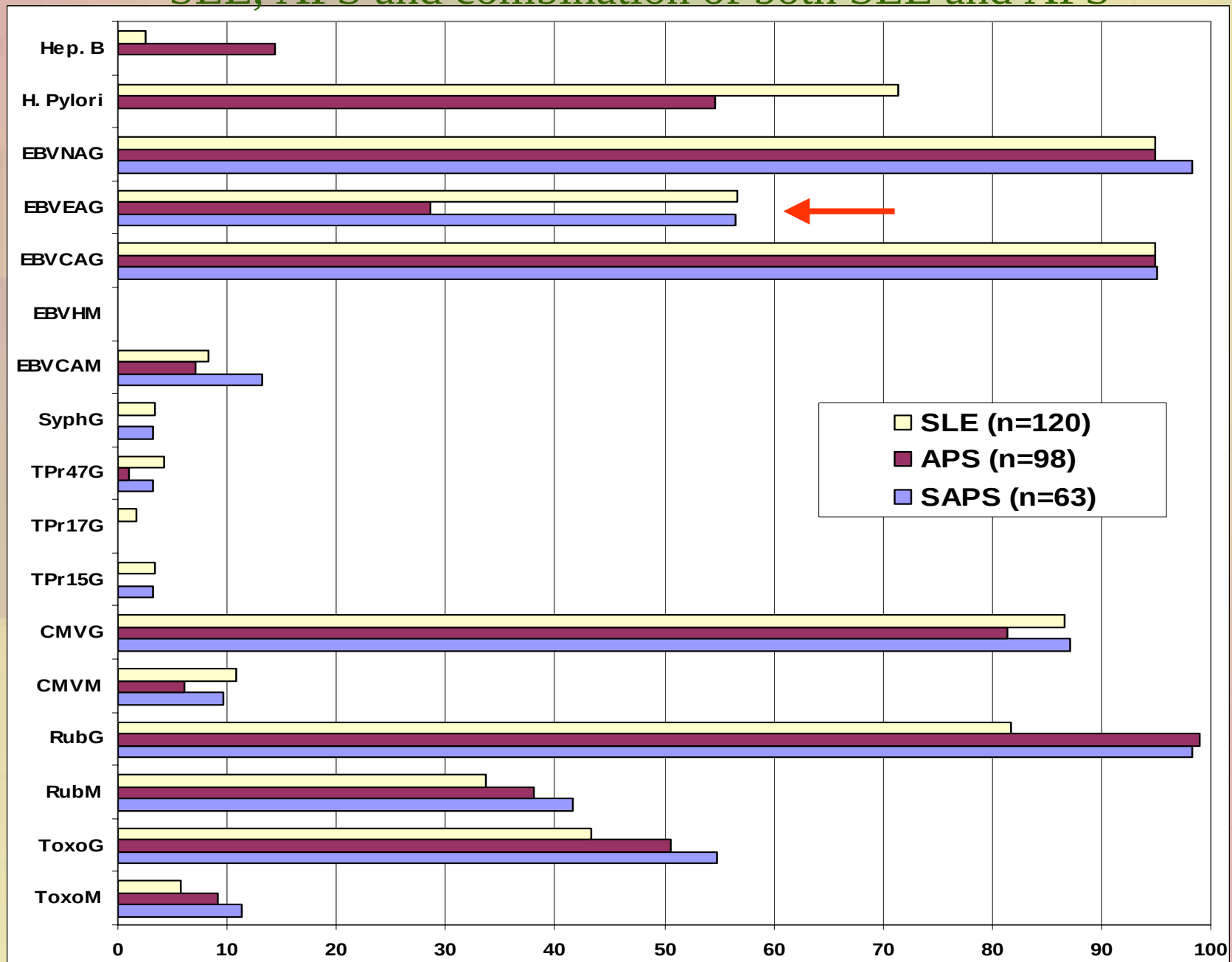
The low frequency of HBV found in SLE, MS and T1D could be the result of:



Protective effect of HBV on the development of these diseases

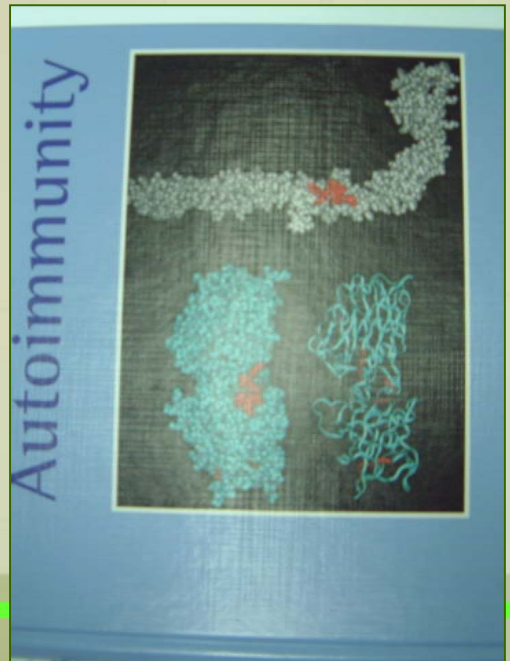
Protective effect of these diseases on the development of HBV infection

Frequency of Infecting Agents Markers in Sera from patients with SLE, APS and combination of both SLE and APS



Antiphospholipid syndrome and infections

Yehuda Shoenfeld



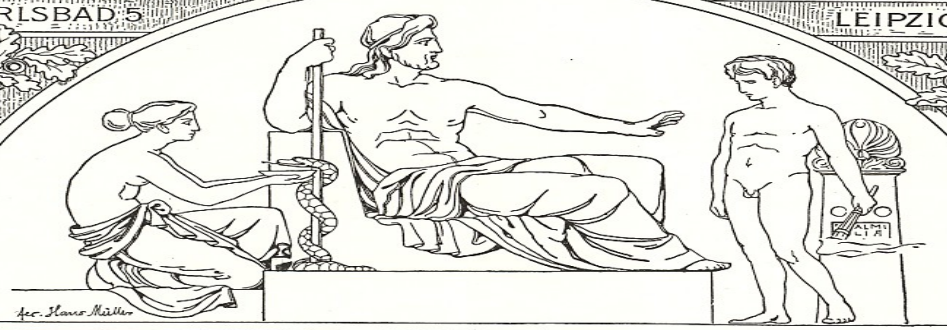
Sypyhilis and Acl (Wasserman reaction)-1906

DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT

BEGRÜNDET VON Dr PAUL BÖRNER

REDAKTEUR: PROF. Dr J. SCHWALBE — VERLAG: GEORG THIEME

BERLIN W. AM KARLSBAD 5 — LEIPZIG, RABENSTEINPLATZ 2



No. 19. Donnerstag, den 10. Mai 1906. 32. Jahrgang.

Aus dem Institut für Infektionskrankheiten in Berlin (Direktor: Geheimrat Prof. Dr. Gaffky) und der Dermatologischen Klinik der Universität in Breslau (Direktor: Geheimrat Prof. Dr. A. Neisser).

Eine serodiagnostische Reaktion bei Syphilis.

Von **A. Wassermann, A. Neisser** und **C. Bruck.**

In den folgenden kurzen Mitteilungen wollen wir über Befunde berichten, die wir an Material von syphilitischen Menschen und Affen erheben konnten.

A. Wassermann und C. Bruck hatten vor einiger Zeit (Medizinische Klinik 1905, No. 55; Deutsche medizinische Wochenschrift 1906, No. 12) darauf aufmerksam gemacht, daß es mit Hilfe der von Bordet, Gengou, Moreschi, Neisser und Sachs bei eiweißpräzipitierenden Seris beobachteten Komplementablenkung gelingt, in Organextrakten und Körpersäften das Vorhandensein einerseits gelöster Substanzen der Mikroorganismen und anderseits spezifischer Antikörper gegen diese Substanzen nachzuweisen. Die genannten Autoren haben diese Methode bereits nach dieser Richtung bei einer Reihe von Infektionskrankheiten (Typhus, Genickstarre, Tuberculose) mit Erfolg angewandt, und es schlug daher der eine von uns (A. Wassermann) vor, nunmehr diese Methode auch für die Serodiagnostik der Syphilis zu erproben. In Ausführung dieses Gedankens wurden nach einem gemeinsam entworfenen Versuchsplan in der dem einen von uns (A. Neisser) unterstellten Klinik Affen mit syphilitischem Virus teils infiziert, teils vorbehandelt und das Serum dieser Tiere, dessen Herstellung wir Herrn Dr. Siebert verdanken, im Institut für Infektionskrankheiten nach der oben genannten Methode gegenüber syphilitischem Material von Kranken und Leichen geprüft.

Diese Methode besteht darin, daß man inaktives Serum der mit syphilitischem Material vorbehandelten Affen mit Organextrakten, Serum etc. syphilitischer Menschen mischt, Komplement (frisches, normales Meerschweinchenserum) zufügt und eine gewisse Zeit binden läßt. Sodann prüft man mittels eines inaktiven, spezifisch hämolytischen Serums und der dazu gehörigen roten Blutkörperchen, ob das zuerst zugefügte Komplement ganz oder teilweise verankert ist. Wenn dies der Fall ist, so dokumentiert sich das in der ganz oder teilweise ausbleibenden Auflösung der roten Blutkörperchen, d. h. in einer Hemmung der Hämolyse.

Diese Hemmung der Hämolyse beweist also, daß Komplement durch die Mischung des Immunserums mit dem Untersuchungsmaterial gebunden worden ist, und wir können daher vorbehaltlich eingehender, hier nicht näher zu erörternder Kontrollen (s. A. Wassermann und Bruck, Deutsche medizinische Wochenschrift 1906, No. 12) aus der Komplementbindung den Schluß ziehen, daß sich 1. in dem durch Vorbehandlung erzielten Immunserum Antikörper befinden und 2. das diesem Immunserum beigefügte Untersuchungsmaterial (Organextrakt) die spezifischen Gegensubstanzen (Antigene) beherbergt. Denn durch das Zusammentreffen des Antikörpers und seines Antigens ist eben Komplement verankert worden, welch letzteres nun zur Komplettierung des hämolytischen Ambozeptors fehlt.

Wenn wir nun unsere Versuche, die wir mit syphilitischem Material angestellt haben, mitteilen, so können wir vorläufig folgendes sagen: Behandelt man Affen mit Blut von sekundär syphilitischen Menschen oder mit Extrakten aus primär-syphilitischen Bubonen und von Condylomata lata oder mit Extrakten aus Organen und Knochenmark hereditär-syphilitischer Kinder und Foeten oder mit Organ- und Knochenmarkextrakten von Affen vor, die 7—8 Wochen nach positiver Impfung getötet wurden, und mischt man diese Sera mit Extrakten aus den Organen hereditär-syphilitischer Kinder und Foeten oder mit den Extrakten aus der Placenta sekundär-syphilitischer Mütter oder mit Extrakten aus Primäraffekten und Condylomata lata oder mit den Organ- und Knochenmarkextrakten von Affen sieben bis acht Wochen nach positiver Impfung, so tritt Hemmung der Hämolyse ein, ein Beweis, daß 1. in dem hergestellten Affenimmunserum Antikörper gegen spezifisch syphilitische Substanzen und 2. in den untersuchten Extrakten diese syphilitischen Stoffe selbst sich befinden. Die Spezifizität dieser Reaktion für Lues beweisen neben den jedesmal nötigen Versuchskontrollen (s. Deutsche medizinische Wochenschrift No. 12) folgende Kontrollen:

1. Das mit syphilitischem Material hergestellte Affenimmunserum wirkt gleichzeitig und in gleichem Maße auf syphilitisches Material von Mensch und Affe, gleichgültig, ob zur Vorbehandlung nur menschliches oder nur Affenmaterial verwendet worden war.

2. Das mit syphilitischem Material hergestellte Immunserum von Affen wirkt nur auf syphilitisches Material von Mensch und Affe, nicht aber auf Körpersubstanzen von nichtsyphilitischen Menschen oder Affen.

Antiphospholipid Syndrom

Immunopathology

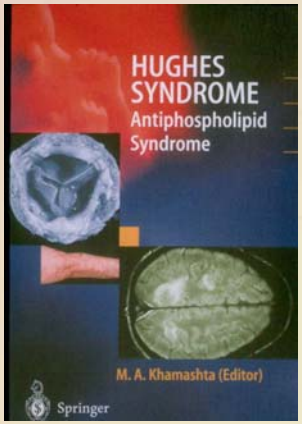
Trophoblast

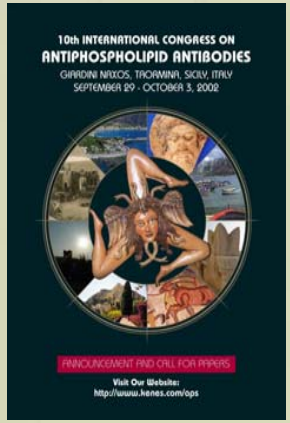
Thrombosis

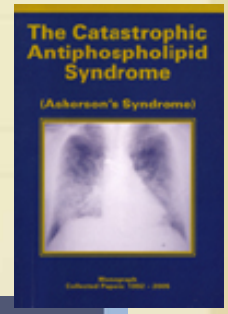
Venous

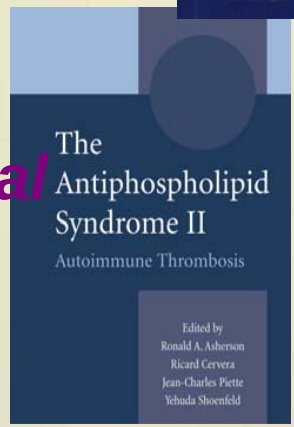
Arterial

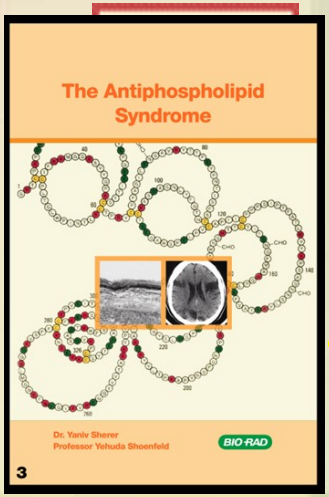
Placental

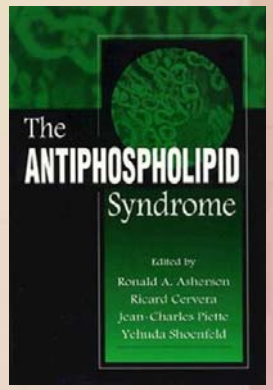










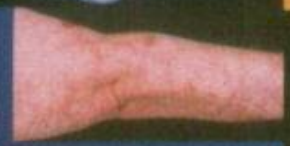


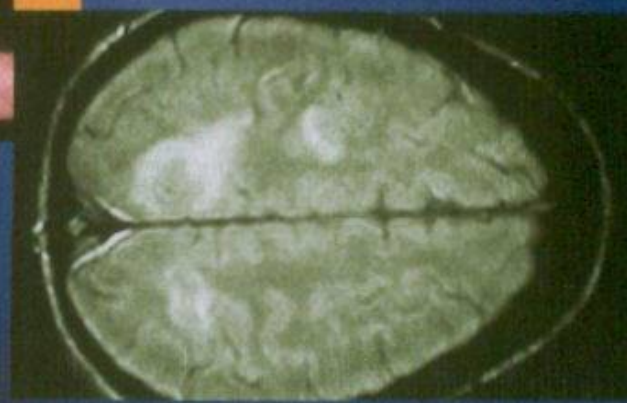
Thrombocytopenia


4 13:49

HUGHES SYNDROME

Antiphospholipid Syndrome





M. A. Khamashta (Editor)

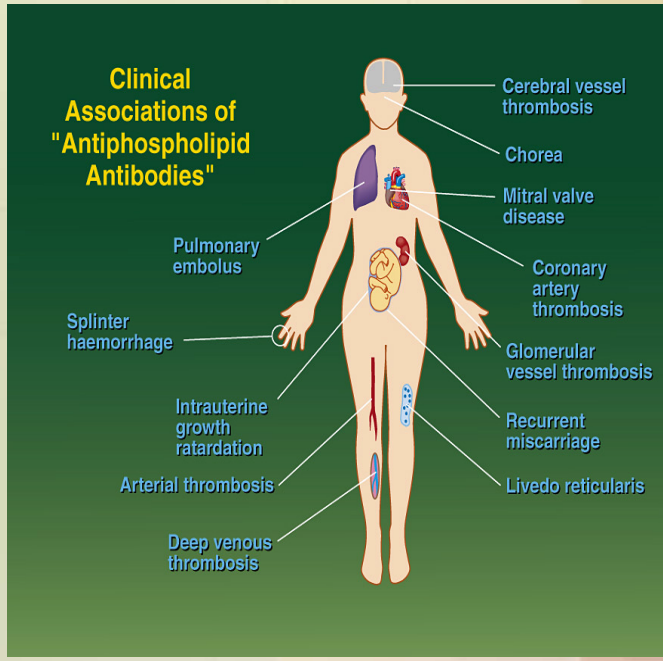
Springer

Systemic APS

Shoenfeld Y. ,Lupus2003;12:497-8

Organs and systems involved in systemic APS (Hughes' Syndrome).

1) Skin (e.g. livedo reticuluris).
2) Heart (e.g. non-verrucal endocarditis).
3) Kidney (e.g. renal artery stenosis).
4) Circulation (e.g. hypertension, atherosclerosis).
5) Lung (e.g. pulmonary hypertension)
6) Brain (e.g. cognitive impairment,memory loss)
7) Brain Vasculature (e.g. migraine).
8) Blood elements (e.g. AIHA, thrombocytopenia).
9) Bone (e.g. osteonecrosis).
10) Adrenals (e.g. apoplexy).
11) Placenta (e.g. insuficiency, fetal death).
12) Pregnancy (e.g. eclampsia, pregnansy loss).
13) Coagulation (e.g. Hypercoagulable state).
14) Blood vessels (e.g. accelerated atherosclerosis).
15) Eyes (e.g. amaurasis fugox, optic neuritis).
16) Ears (e.g. acute hearing loss).
17) GI involvement (e.g. spleen, Budd Chiari).
18) Orthopedics



2006

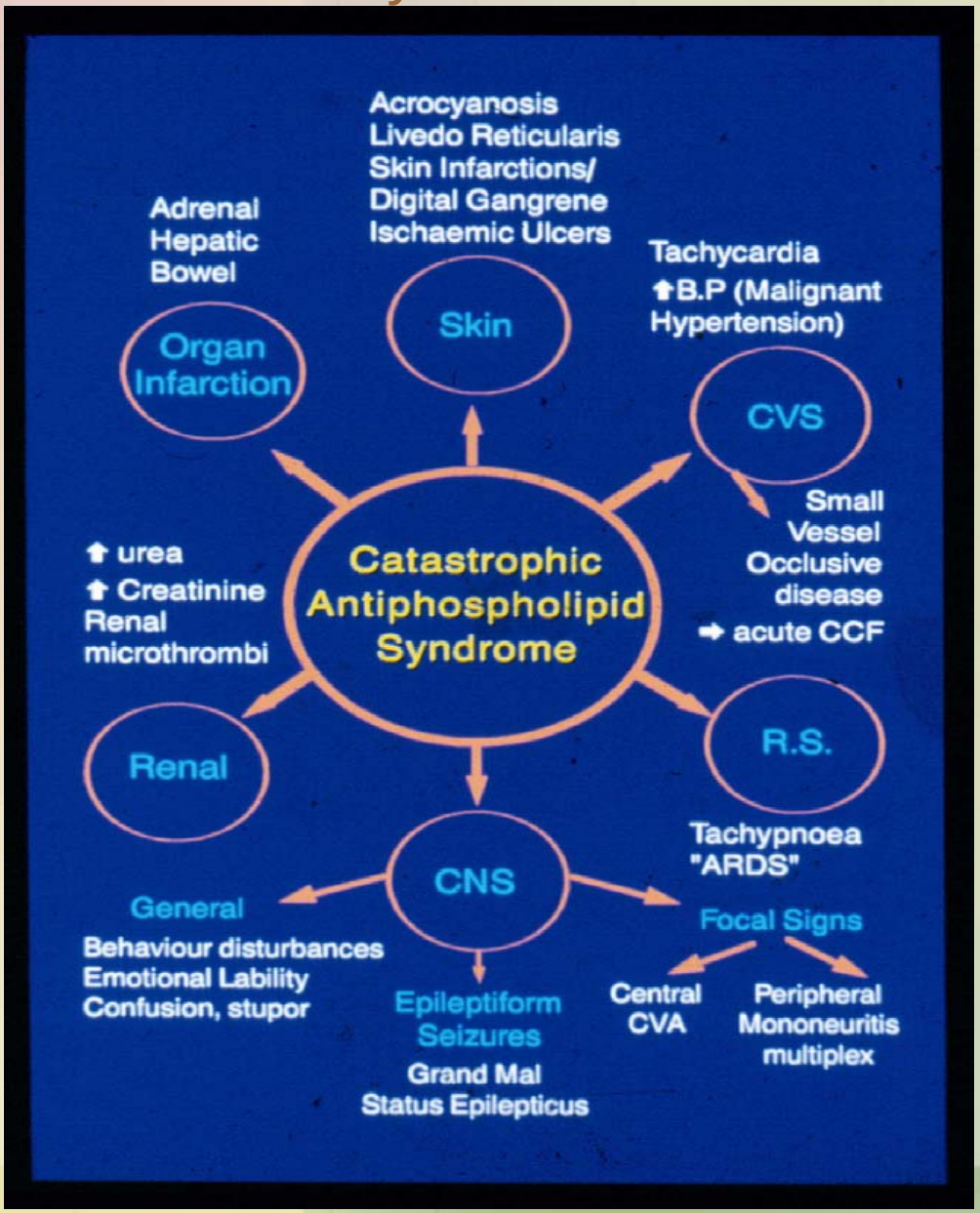
19) Renal and celiac arteries stenosis
20) Fractures

Etiology and pathogenetic mechanisms of the anti-phospholipid syndrome unraveled.

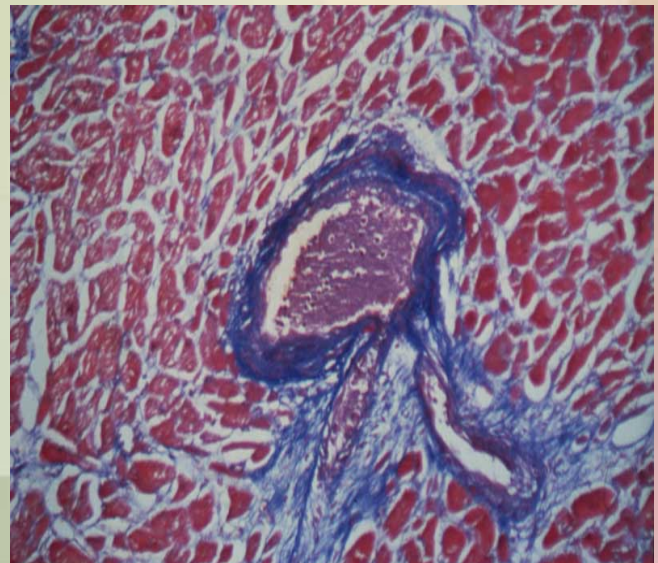
Shoenfeld Y.

Trends Immunol. 2003;24:2-4

The Catastrophic Antiphospholipid Syndrome:Manifestations: 1992



The Asherson's syndrome

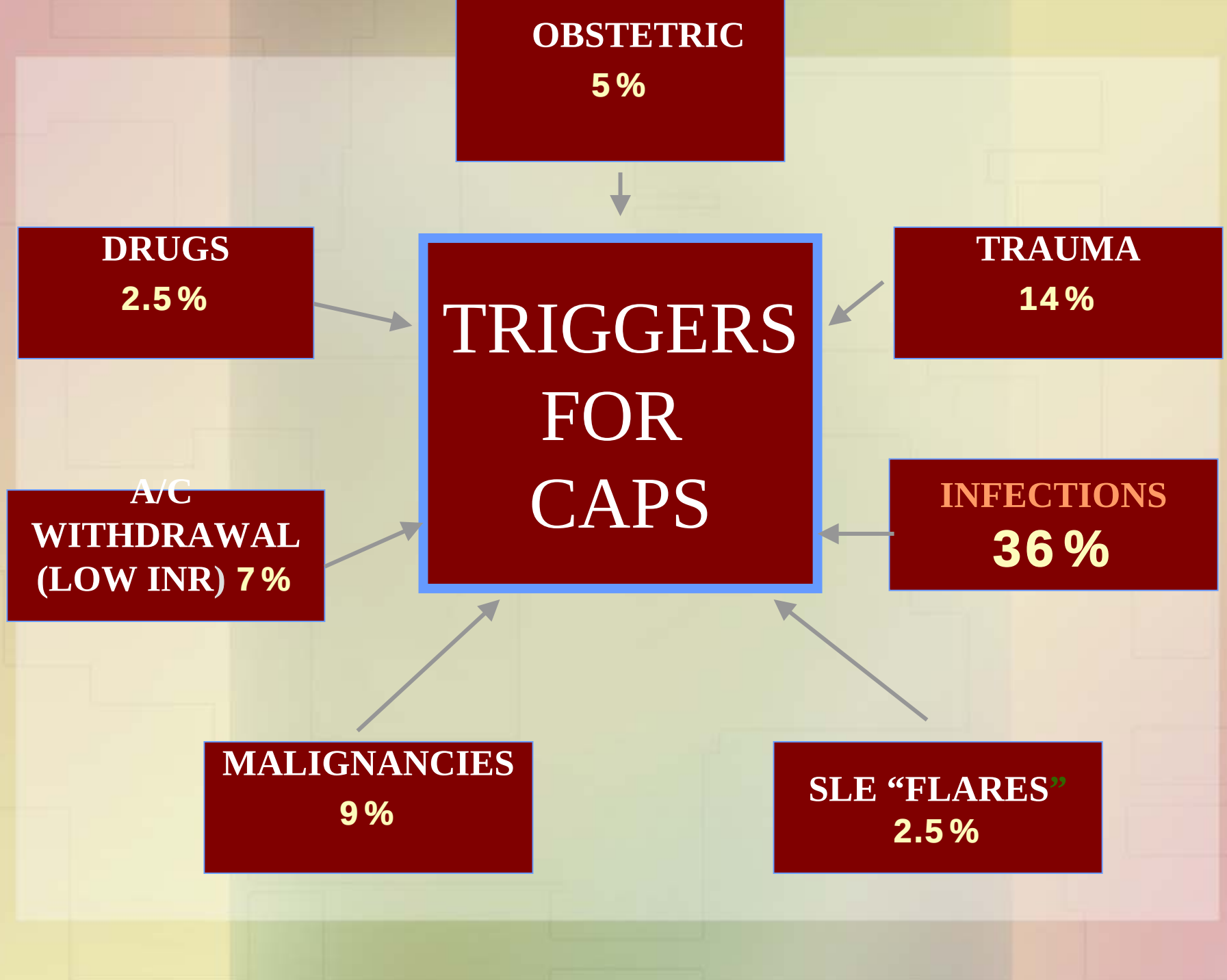


CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Role of Infections

The Journal of
Rheumatology

The Role of Infection in the Pathogenesis of Catastrophic Antiphospholipid Syndrome — Molecular Mimicry?


OBSTETRIC
5%
DRUGS
2.5%
TRIGGERS FOR CAPS
TRAUMA
14%
A/C WITHDRAWAL (LOW INR) 7%
INFECTIONS
36%
MALIGNANCIES
9%
SLE "FLARES"
2.5%

APS - infectious disease

Infectious associated aPL with thrombosis

1) EBV - *J Pediatr 128: 319, 1996.*

2) Leprosy - *Int J Lep Myc Dis 66:387,1998.*

3) CMV - *Clin Infec Dis 24: 197, 1997*.

4) HIV - *Eur J Clin Invest 28: 115, 1998*.

5) HCV- *Eur J Hepatology 23: 199, 1997*.

6) Adenovirus - *Ann Hematol 67: 95, 1993*.

Prevalence of aCL in bacterial, rickettsial, & spirochetal infections*

Infection/Organism	No. of patients	Frequency (%)	Isotype
Typhus	NG	20	-
Leprosy	99	33-67	IgG, IgM, IgA
TB	60	27-53	IgG, IgM
Bacterial endocarditis	92	5-44	
Streptococcus pyogenes	81	0-80	
Mycoplasma pneumonia	175	20-53	IgG,
S. aureus	21	43	IgG,
Streptococcus	20	80	IgG,
Salmonella	20	60	IgG,
E. Coli	6	67	IgG,
Ornithosis	9	33	IgG, IgM, IgA
Q fever	38	42-84	IgG, IgM
Leptospirosis	16	50	IgG
Lyme disease Borrelia	364	14-41	IgG, IgM

Viral infections and clinical manifestations of APS

Infectious agent	Anti-cardiolipin	β2GPI	APS manifestations
HCV	IgG	+	Thrombosis
Varicella	IgG, IgM	-	PE*, thrombosis
Parvovirus B19	IgG	+	Thrombosis
CMV	IgG, IgM	-	Thrombosis
HTLV-1	IgA	-	-
HIV	IgG, IgM, IgA	+/-	Leg ulcer necrosis, thrombosis

* PE- pulmonary embolism


CAPE OF GOOD HOPE
THE MOST SOUTH—WESTERN POINT
OF THE AFRICAN CONTINENT
18° 28' 26" EAST
34° 21' 25" SOUTH

Case Report Prediction?

Mother- APS, Vitiligo

Daughter- 22 yo, healthy, ANA 1; 160, LAC, IgA anti CL, Pills??

Infec Mono??


Audi Centre Cape Town
A4
1.8T
CA 130-557

B2GPI

NORTH CAROLINA

Anticardiolipin antibody

Takao

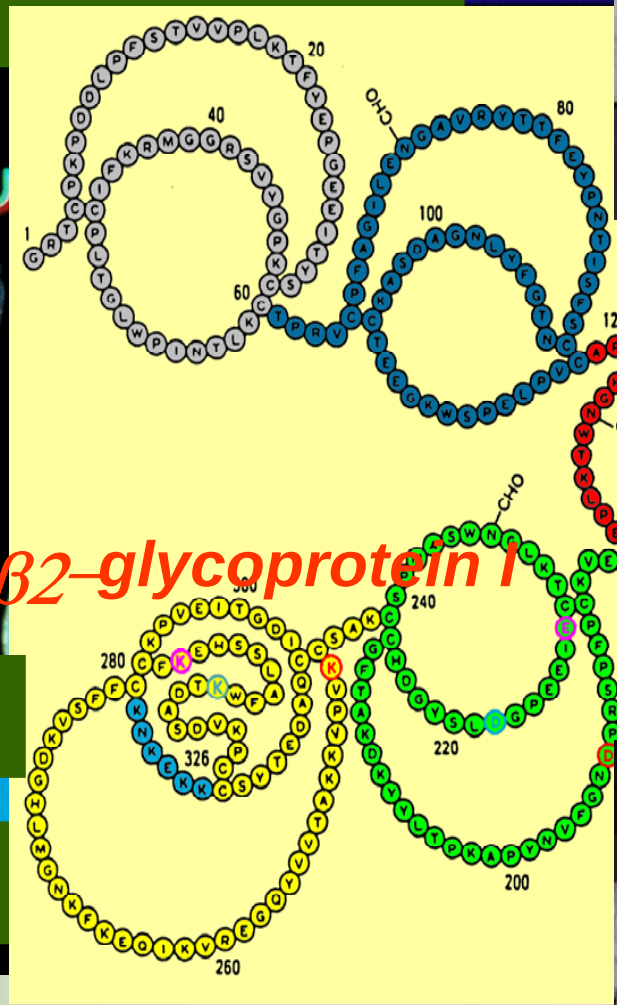
ジオリピン抗体の特異性

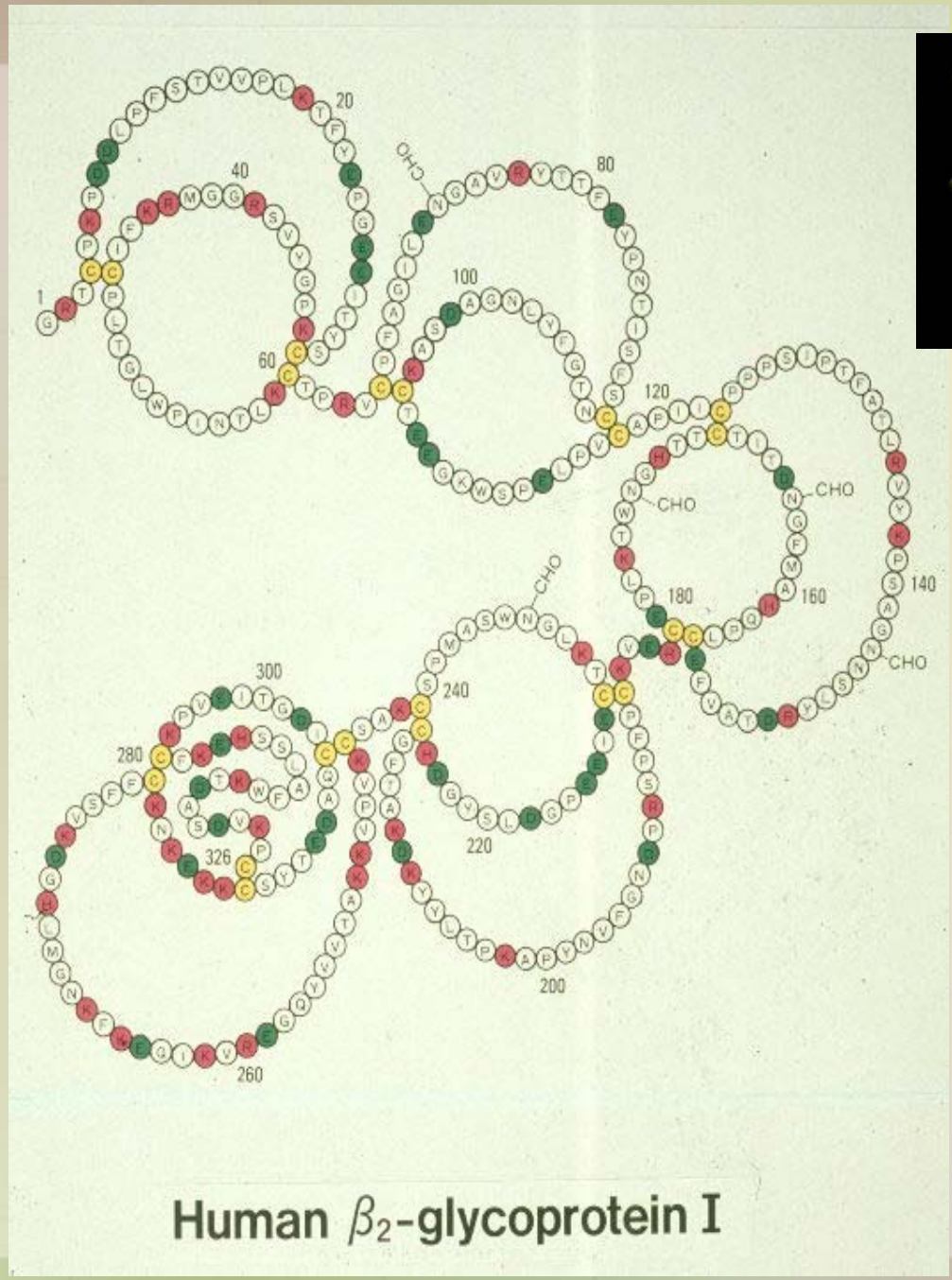
抗カルジオリピン抗体

Anticardiolipin antibody

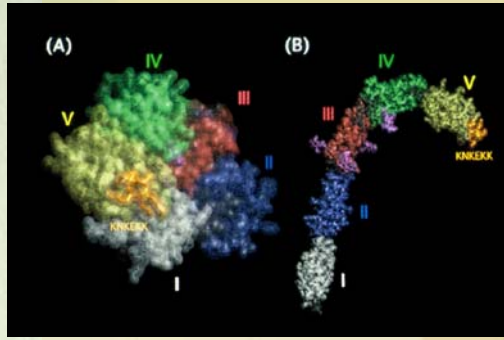
カルジオリピン

Cardiolipn



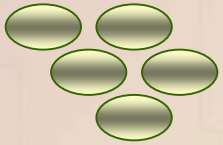


Human β_2-glycoprotein I




Dreksen

Targeting β2GPI corresponding peptide epitopes for anti-β2GPI

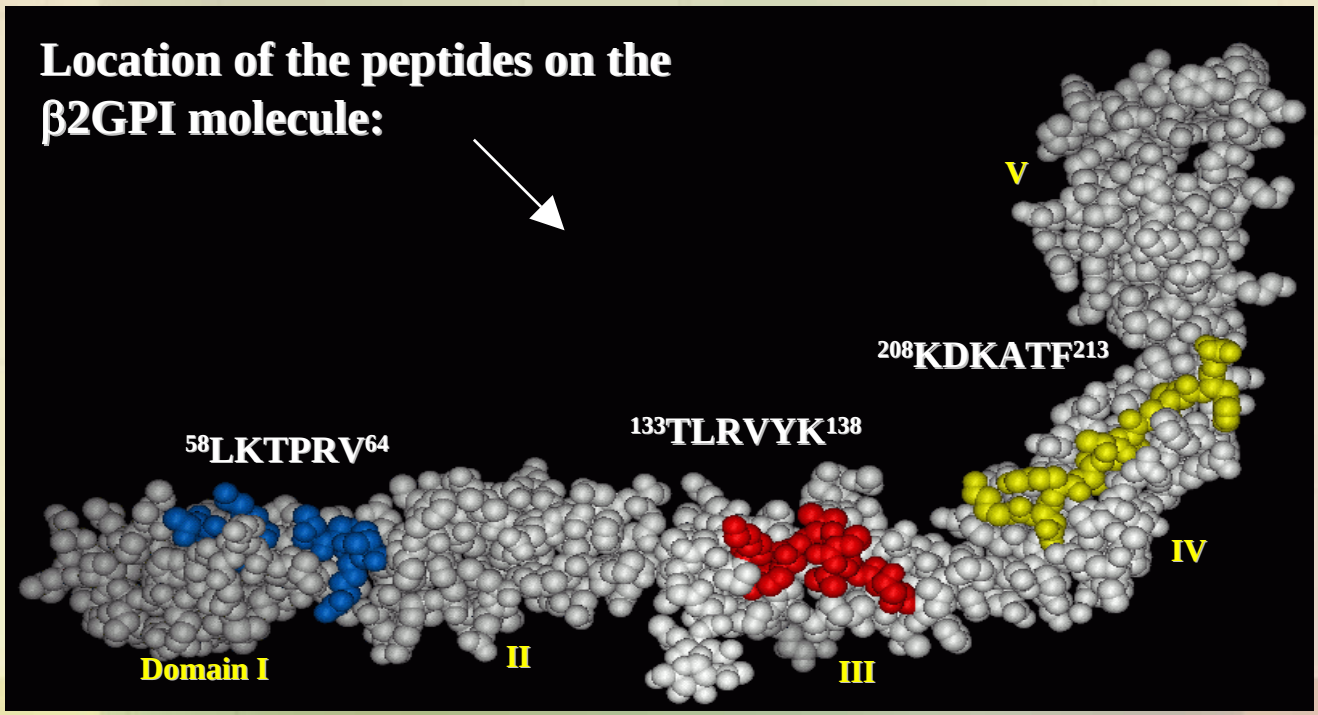


Human B cells from APS patient

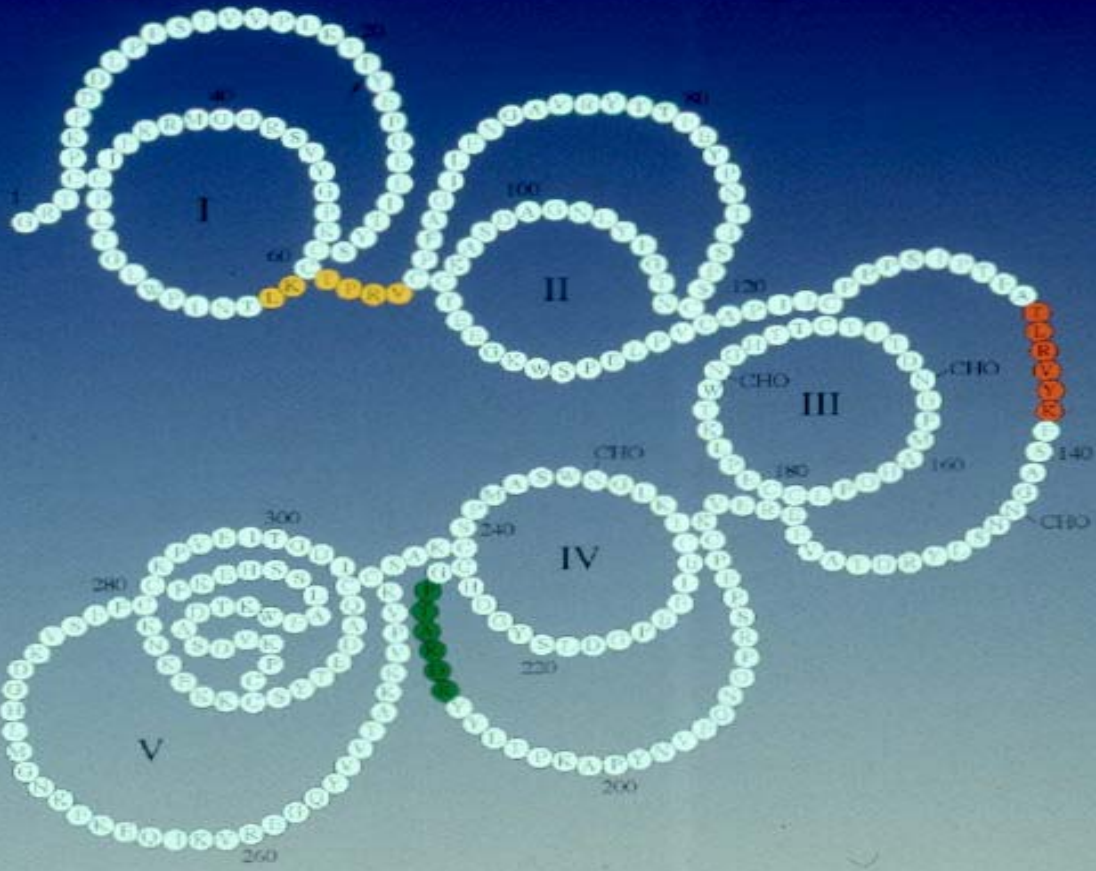
Fusion with heteromyeloma

Hybridoma cells producing anti-β2GPI Abs

β2GPI related synthetic peptides



β2GLYCOPROTEIN-I EPITOPES , ISOLATED FROM A HEXAPEPTIDE PHAGE-DISPLAY- LIBRARY



MIMOTOPE: LVEPWR

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 5164–5168, April 1999
Immunology

Prevention of experimental antiphospholipid syndrome and endothelial cell activation by synthetic peptides

(anti- b2glycoprotein-I-peptide phage display library-anticardiolipin)

MIRI BLANK*, YEHUDA SHOENFELD*, SHMUEL CABILLY †, YEHUDIT HELDMAN †, MATI FRIDKIN ‡, AND EPHRAIM KATCHALSKI-KATZIR †§

*Research Unit of Autoimmune Diseases, Department of Medicine "B," Sheba Medical Center, 52621, Tel-Hashomer and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and † Departments of Biological Chemistry and ‡ Organic Chemistry, The Weizmann Institute of Science, 76100 Rehovot, Israel

A: NTLKTPRVGGC,

B: KDKATFGCHDGC,

C: CATLRVYKGG,

Homology between the studied peptides and various microbial pathogens

	LKTPRV	TLRVYK
Bacteria	*Pseudomonas aeruginosa*	*Sreptococcus pneumonia*
	Yersinia pseudotuberculosis	*Shigella dysenteriae*
	Haemophilus influenzae	
	Neisseria gonorrhoeae	
Viruses	*Cytomegalovirus (CMV)*	*Epstein-Barr virus (EBV)*
	Polyoma virus	
	Adenovirus-40	
Yeasts	*Streptomyces lividans*	*Candida albicans*
	Saccharomyces cerevisiae	
Parasites	*Schistosoma mansoni*	
		Tetanus toxoid

INDUCTION OF *EXP.APS* IN NAIVE MICE : β2GPI EPITOPE MIMICRY WITH BACTERIAL PARTICLES

- Tetanus toxoid
- Microbial particles

Mouse IgG

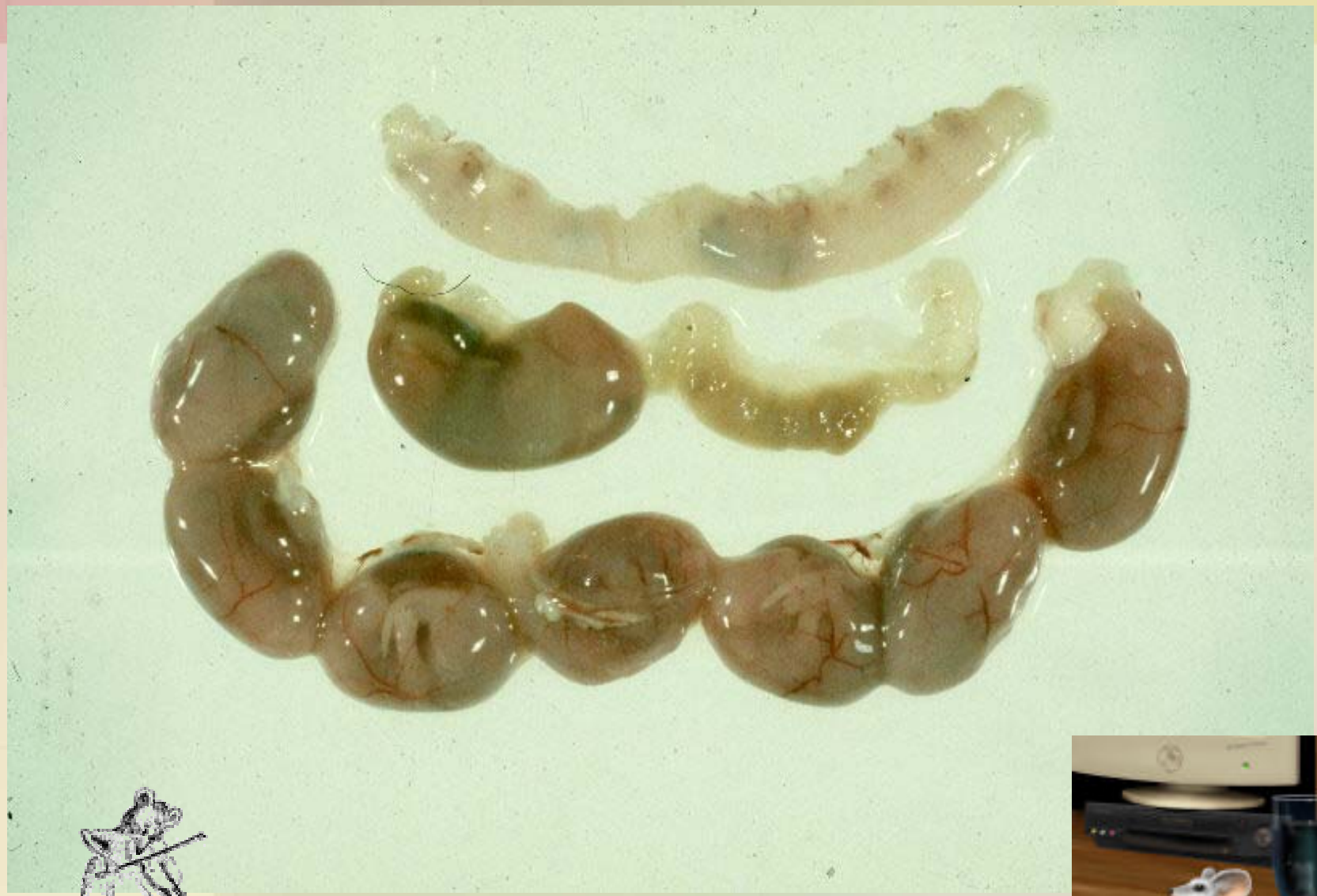
β2GPI/peptide column

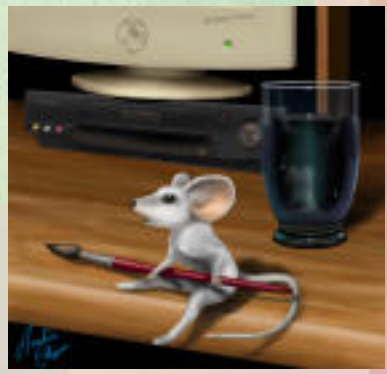
Infusion

Anti-peptide Abs

Exp.APS

- Fetal loss
- Thrombocytopenia
- aPTT





The infectious origin of the antiphospholipid syndrome (APS): induction of exp.APS by passive transfer of anti-β2GPI Abs induced by common bacteria

Blank M, Krause I, Levy Y, Fridkin M,

Keller N and Y Shoenfeld

J Clin Invest 2002

eular 2005
vienna
8-11 JUNE 2005

EULAR CONGRESS NEWS

6TH ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY | JUNE 8–11, 2005 | AUSTRIA CENTER VIENNA

Thursday Edition

JUNE 9, 2005

8:15 – 9:45
State-of-the-Art / Best Practice
Plenary session: Advances in major rheumatic diseases — Hall A

10:15 – 12:00
Top Abstract Session
Cutting edge in rheumatology 1 — Hall A

Abstract Sessions
Advances in RA therapy — Hall D
Advances in imaging — Hall E
Advances in spondyloarthritis — Hall F
Advances in osteoarthritis — Hall B
Advances in outcomes science and economics — Hall C
Advances in paediatric rheumatology — Hall G/H
Advances in muscle, fibromyalgia and pain — Hall I/K
Advances in cellular autoimmunity — Hall L/M
Advances in biological therapies — Hall N/O
Advances in vasculitis — Hall R
Advances in autoimmunity and genetics — Hall Q

Meet the Standing Committee
Social Leagues Round Table: Campaigning — Hall P

Allied Health Professionals
Abstract Session: Allied Health Professionals — Hall S

13:30 – 15:00
Clinical Science
Evolving aspects of spondyloarthritis — Hall A
Advances in imaging—new techniques

EULAR Prize 2005 Recipients Home in on Antiphospholipid Syndrome's Triggers

In their EULAR prize-winning research, Professor Yehuda Shoenfeld, MD, FRCP (Hon.), Professor Ricard Cervera, MD, PhD, and Professor Pier Luigi Meroni, MD, have been collaborating for years to address the question of etiology: What causes antiphospholipid syndrome (APS) to develop in some people, but not in others?

In pursuit of an answer, they started with what is known about other autoimmune conditions: "that in addition to genetic preponderance there needs to be some kind of environmental factor to trigger disease and determine when it will develop," said Prof. Shoenfeld of the Sheba Medical Center, which is affiliated with the Sackler Faculty of Medicine at Tel Aviv Uni-

Yehuda Shoenfeld, MD, FRCP (Hon.)

Ricard Cervera, MD, PhD

Pier Luigi Meroni, MD

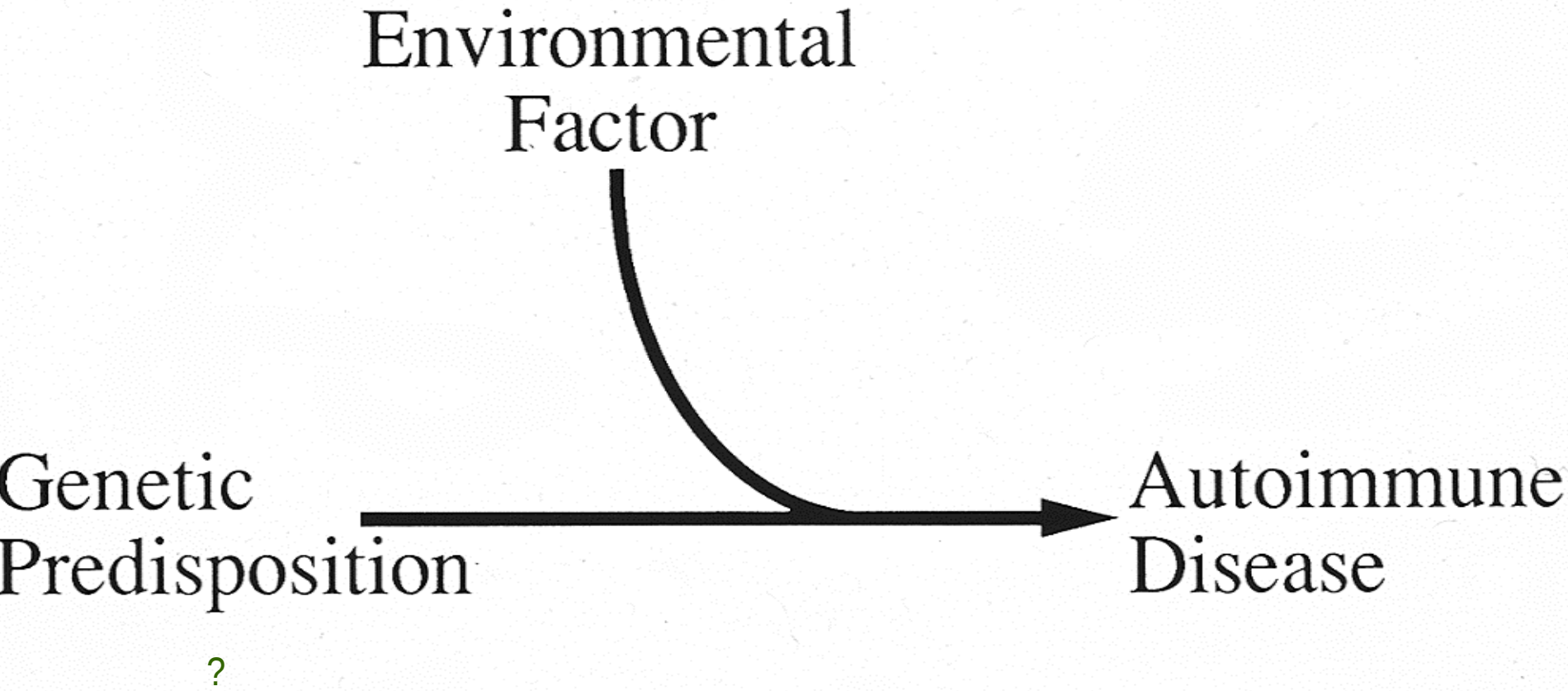
triggers of autoimmune disease include drugs and infecting agents. However, because it is rare to find drugs as the trigger in APS, he and his colleagues focused their investigation on the role of infecting agents.

Case reports indicate that there is "a time relationship between infection and [the] appearance of catastrophic APS," he said in an interview with EULAR

vessels all over the organs, as well as organ collapse, which results in death in nearly 50% of patients, regardless of treatment.

When Prof. Shoenfeld and his colleagues analyzed a large series of these rare cases, they found that "in close to 40% of the cases there was some kind of an infection preceding the catastrophe." Infections in these cases ranged from influenza or the common cold, to AIDS or sepsis. "This led us in the direction of doing more molecular biological research," he said.

"We studied the autoantibody implicated in APS as a vehicle to analyze disease causes. ... We subjected the antibody to a phage library display, and we fished out three, and then nine, peptides from


Environmental
Factor
Genetic
Predisposition
Autoimmune
Disease

?

HLA association of anti- β2GPI

HLA - DQB1 * 0302 (DQ8)

HLA - DQB1 * 03 allels

HLA - DQB1 * 0301,*0302,*0303

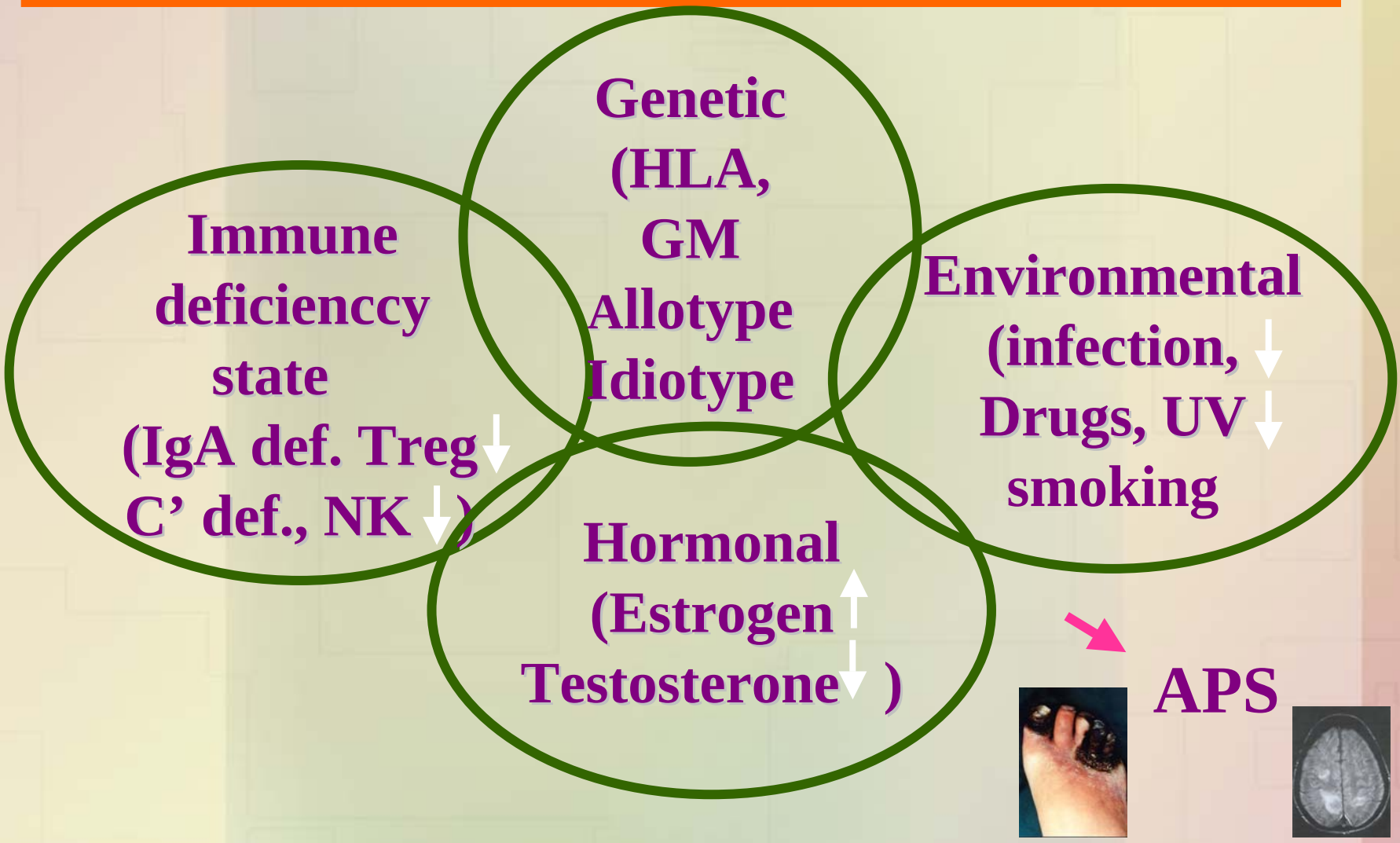
Blocks: HCA-DR6

Mexican: HLA-DR53

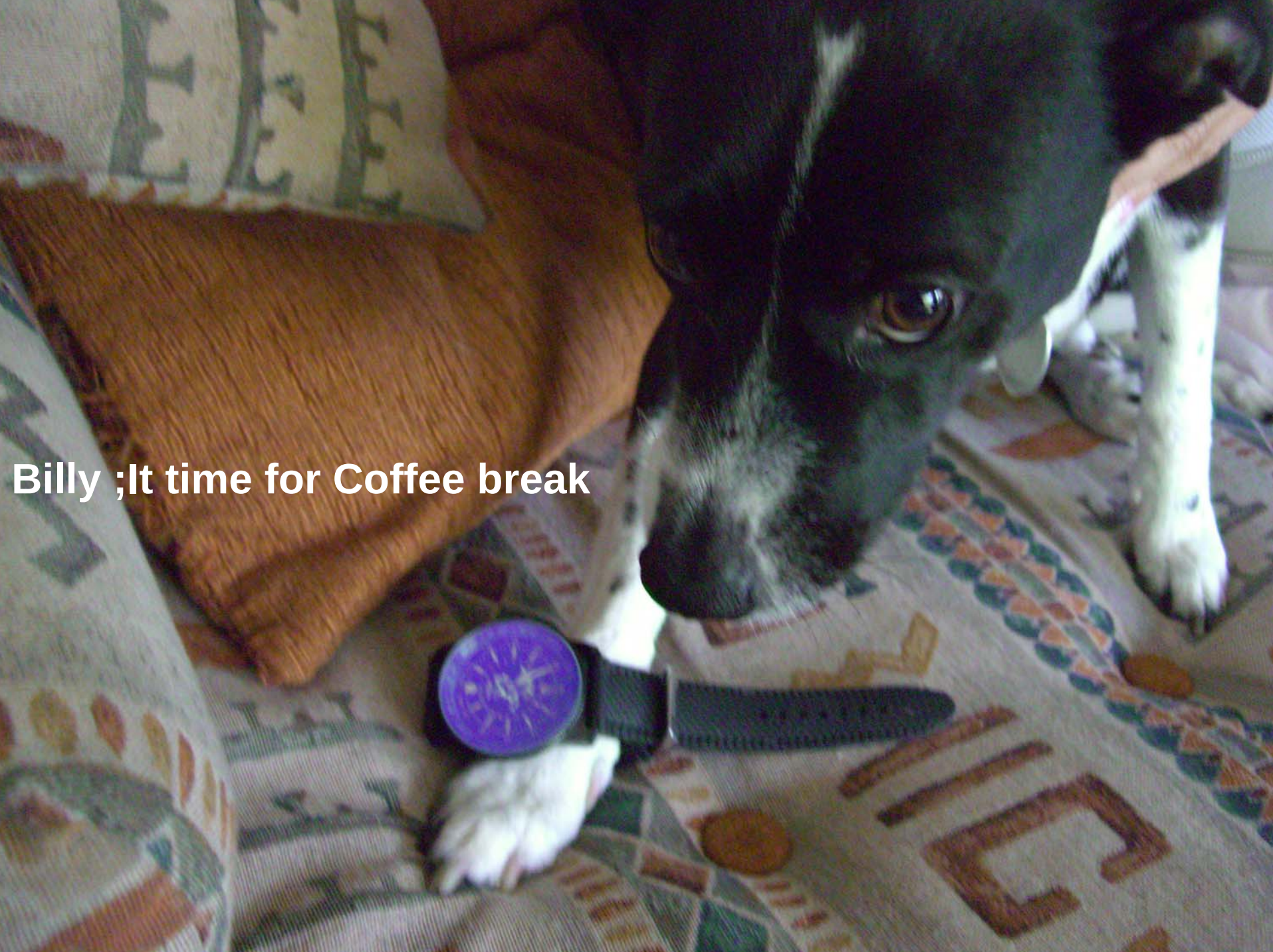
Arnett FC, et al: A & R 1999: 42: 268-274

autoimmunity

Yehuda Shoenfeld MD



"..APS joins other classical autoimmune diseases as being associated and induced by common infectious agents…"


Billy ;It time for Coffee break