



Editorial

Geo-epidemiology and autoimmunity

A B S T R A C T

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Autoimmune disease (AD) affects approximately 3% of the population. This is an enormous number, but ironically the study of autoimmunity has not taken on the significance of many other diseases because so many of the ADs are relatively uncommon. Indeed, despite enormous advances in the diagnosis and the treatment of AD, there is still a paucity of data on the etiological events that lead to the clinical pathology. For most other human diseases, the etiology is addressed and often solved by the use of epidemiology. Epidemiology consists of the study of prevalence of a disease, coupled with analysis of genetic factors and detection of environmental agents. In the context of autoimmune conditions, preclinical epidemiology has recently been favored, as a consequence of the discovery that autoantibody precedes overt disease. The idea of a North–South gradient in the prevalence of ADs, with a reciprocal gradient in that of infectious injuries has proven to be debatable. More importantly, environmentally-induced changes have been shown to modify certain diseases giving rise to the key concept of epigenetics. However, it is clear that major voids exist. Some of these voids were hoped to be solved by the use of genome-wide associations. This, however, has proven very problematic, as the genetic basis of AD is considerably more complicated than once believed. We now base our hopes on next generational sequencing as a brut force undertaking to partially decipher the genetic code that predisposes individuals to AD. This volume is a compilation of papers in Autoimmunity Reviews and the Journal of Autoimmunity and presented as part of the 7th International Congress on Autoimmunity in Ljubljana, Slovenia. It is clearly impossible to present data on the geoepidemiology of all of the AD. Instead, we attempted to generate interest amongst immunologists to generate papers that are thought provoking but also contemporary reviews.

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1. Introduction

This volume is based on the goals of the 7th International Congress on Autoimmunity. The venue for the conference is in Ljubljana, Slovenia and offers physicians and scientists interested in autoimmunity an advanced, stimulating scientific program. Within that program will be featured updated and diagnostics, pathogenesis and therapy. This Congress, much as in previous Congresses and satellite meetings, will include a book in the registration bag of every participant. Papers from the Congress will also be published in the official journals of the meeting, Autoimmunity Reviews and the Journal of Autoimmunity. Previous Congresses have focused on publication of key issues of interest to autoimmunologists, including for example protective auto-antibodies (Abs), epigenetics [1], T regulatory cells [2], bone marrow transplantation to treat autoimmune diseases (AD) [3,4], the anti-phospholipid Ab syndrome (APS) [5,6], infection and autoimmunity [7–10], as well as discussions of specific AD that offer lessons for human immunopathology [11–14]. At this meeting, the focus is on geoepidemiology and the series of papers which follow within this issue are intended to revolve around this theme of environmental factors, prevalence and incidence, but also discussion of unique triggers such as nanoparticles and drugs.

This volume is dedicated to the founding principles and the good work of the American Autoimmune Related Diseases Association (AARDA). AARDA plays a fundamental role throughout the world in education, awareness, and research in developing new therapies, improved diagnoses, and support services for patients with AD. AARDA has in fact become an international healthcare organization. The seed for AARDA was planted by Virginia T. Ladd, who is not only the founder, but also the current president. Virginia Ladd, herself a sufferer of AD, became involved with the Lupus Foundation of America and the Lupus Chapter in the State of Michigan. In her role within the Lupus Foundation, Virginia Ladd became involved addressing questions from patients and family that were desperate for information. Over time, she became ever more knowledgeable and became a resource for patients seeking information on a variety of AD. For Virginia, who sought no recognition for herself, there was a compulsion to help not only because of her own health, but also the presence of AD within her family.

In the late 1980s while President of the Lupus Foundation of America, Virginia Ladd became convinced of the need to focus research more in the broad area of AD but, more importantly, to develop the understanding that such research and its funding

was dependent on patient education and public awareness. She was also aware that a huge segment of the healthcare field, represented by AD, did not appear to have an American national focus or clearinghouse for the large number of AD identified. Autoimmunity was little known to the public and almost no collaboration existed amongst national health agencies in the areas of research, public education and patient services. Even though Virginia Ladd is not a trained scientist, she recognized that such diseases share common pathways and likely similar genetic backgrounds. In discussions with many professionals in the field, she felt there was an urgency to develop advocates for basic research and public awareness. Finally, the steering committee of community leaders was organized to initiate an American national agency for all AD. Supported by a dedicated cadre of people who shared her vision, the American Autoimmune Related Diseases Association was founded in 1990, based in part on a skeleton staff and dedicated volunteers. In December 1991, the American Autoimmune Related Diseases Association was incorporated and received its 501(c)(3) designation from the Internal Revenue Service. It was, in fact, the first national non-profit health agency that would serve the interest of the millions of Americans suffering from AD. In 1992, AARDA formed its prestigious Scientific Advisory Board which was chaired by the Dr. Noel Rose of Johns Hopkins University who contributed significantly to the research of AARDA. AARDA is now approaching its 20th anniversary and has remained the national leader not only in patient education, advocacy, and public information, but also in developing national workshops, discussion groups, symposia and direct funding of research. The progress report on a recent workshop was published in 2008 [15]. It is for this reason that this volume is dedicated to Virginia Ladd and AARDA and the chairpersons of this symposia are proud and excited to recognize the achievements of AARDA and the mission they are fulfilling.

2. The discipline of autoimmunity

Much has been written about the unique discipline of autoimmunology from the perspective of a physician skilled in clinical immunology [16].

Taken individually, ADs, which give rise to chronic morbidity and significant disability, are uncommon, yet these disorders, taken as a group, represent the leading cause of death among middle-aged women [17]. On one side, a number of disorders, such as pancreatitis, reproductive failure or inflammation-induced atherosclerosis, have recently been presumed as autoimmune. On the other side, epidemiological data have been newly generated in countries, such as China [18]. Although such or an awareness constitutes already an epidemiological thought-process, this approach turns out to be so diffuse that, in any textbook of medicine, epidemiology is often a section gathering clinical features, and risk factors based on case reports and case series. This discipline has even been portrayed as an art [19]. Brilliant technical and methodologic advances have been accomplished in this art over the last decade, and epidemiological analysis described by Lilienfeld [20] as the study of prevalence of a given disease in human populations, coupled with the identification of factors that influence its geographic distribution. Defining the descriptive epidemiology of these conditions will provide clues to risk factors and identify areas to allocate public health and research resources. In 1997, a seminal work compiled the results accumulated over the former 30 years on 24 autoimmune entities worldwide. This meta-analysis estimated the overall prevalence of autoimmunity at 3% [21]. There was a concomitant claim that this prevalence reached 5% [22]. Both estimates were, however, limited by the lack of recent data for many diseases, and hence based on unreliable conclusions.

3. The concept of risk

Analytic epidemiology deals with the concept of risk. In this respect an exciting body of research has then pointed out that, for autoimmunity to occur, the genetic background warrants to be combined with environmental injuries. New insights into the genetic susceptibility to autoimmune disorders have thus been gained, with a host of established and putative risk factors for all AD. Of note, only a proportion of them are specific for a given pathological condition. Since then, have we made progress?

The difficulty in making the diagnosis of certain AD has discouraged epidemiologists. The classification criteria of primary Sjögren's syndrome (pSS) have raised an endless problem. Albeit frequent, these conditions have aroused to so few epidemiological studies that the estimated prevalences are highly divergent. In spite of such discrepancies, the scientific community gets aware that the way to delineate the prevalence has greatly improved over the last years. A new generation of statistical tools, such as systematic reviews and meta-analyses, have enabled comprehensive analysis of the total burden represented by this collection of disorders [23,24].

4. Geographic aggregates

The frequency of ADs differs from country to country (Table 1), and geographic aggregates have been delineated. For example, disparities in incidence, severity and outcomes of pSS, primary biliary cirrhosis [25] and systemic lupus erythematosus (SLE) have been conceived as alarming. Numerous variables, including the criteria of the disease in study, account for such variations since the incidence rates of SLE fluctuate from under 1 to over 10 per 100,000 person-years. This reality is the *raison d'être* of epidemiology. The archetype of autoimmune settings has been recognized in all continents, but, although a rarity or a yet to be investigated entity in Africa, it is extremely common in African descent around the world. Hopkinson et al. calculated a hazard ratio of 4.4 for Afro-Caribbeans to develop renal SLE, compared with Caucasians [26]. Unfortunately, only little data are available on the prevalence of disease-associated autoAbs in each general population, their variations by age, sex, ethnicity and other demographic features.

Preclinical epidemiology is being acknowledged as presenting more and more importance. A handful of studies are available regarding the outcome on normal autoAb-bearing individuals. Remarkably, rheumatoid factor (RF) precedes the onset of rheumatoid arthritis (RA), as determined by nationwide welfare program in Scandinavia [27]. We know now that normal individuals with anti-DNA Abs suffer from overt SLE later on, as established by the exemplary epidemiological study consisting in analysis of serum samples of 130 persons obtained in the repository of in the American Armed Forces personal, years prior to the onset of the disease [28]. Anti-phospholipid Abs have also been detected long before the development of thrombosis in APS and SLE patients [29]. Thus, specific

Table 1

Geographic area-related variation in the prevalence of certain autoimmune diseases.

Disease	Rate per 100,000	Area
Systemic lupus erythematosus	34–150	US, Spain, Greece
	42	Canada
	45	Australia
Multiple sclerosis	177–358	US, Canada
	101	Turkey
	46	Norway
Sjögren's syndrome	600	Greece
	110	Denmark
	3500	UK

autoAbs, such as RF, anti-cyclic citrullinated peptide Abs precede the symptoms of RA throughout serial measurements in blood donors [30]. Such clues as to sub-clinical conditions are needed in pSS owing to the length of the interval between initiation of the autoimmune process and awareness by the patients themselves of the consequential sicca symptoms, and therefore their complains and willingness to be referred to the hospital [31].

On the other hand, there are now strong evidence from studies of epidemiology, often based on differences in geographic regions, as well as variations in extrinsic factors that have been shown to influence the emergence and progression of disease. However these environmental factors often explain only a small number of cases, and, on their own, they are not sufficient to cause the disease.

5. Genetic variation

Genetic polymorphisms contribute mostly to autoimmunity susceptibility, and thereby underly ethnic differences in the presentation of the disease, or the severity of its symptoms [32]. Johnson et al. have shown, in a cross-sectional analysis of SLE patients from Brazil, Sweden and England, that non-Caucasians had more active disease than the remainder [33]. Furthermore, a myriad of new candidate genes have been identified. In line with these genetic findings, numerous family studies have revealed that SLE and RA afflict members at a greater rate than in the general population [34]. Overall, clustering of autoimmune conditions support a genetic contribution to diseases, yet, despite advances in allele sharing and other linkage methods, the imprecision of heritability estimates and potential biases explain that little inferences can be drawn from family studies. Similarly, ethnic differences exist in autoimmunity genetic predisposition. For instance, in North America, blacks are at higher risk for SLE than whites. If one takes the other example of RA, geographic variations have been described in cohort of 83,546 American women [35], possibly due to regional variations in behavioural factors, climate and environmental exposures. Importantly, this pattern is not consistent for all the ADs [36].

Obviously, only a minority of genetic variations are expected to be highly penetrant. However, the combined proportion of the variance in RA susceptibility conferred by the shared epitope alone far outweighs that conferred by all the other susceptibility loci put together. Thus, based on heavy technologies, impressive progress has been accomplished. Genome-wide association analyses using gene chips have thus allowed hundreds of thousands of single-nucleotide polymorphisms (SNPs) to be investigated. The obvious advantage is the opportunity to pitch into non-suspected genes. In return, large numbers of hints require validation. These systematic studies have pinpointed a number of predisposing genes acting in sequence or in parallel. Disappointingly, the non-HLA SNP markers associated with various disorders account for a small contribution to the total variance in susceptibility.

One step further, these observations, as well as the sharing of common idiotypes [37], do not necessarily mean that all diseased relatives suffer from the same pathology as their proband who justified the selection of the family. Furthermore autoAbs found in family members are not necessarily pathogenic. Rather than disease-specific genes, there may be autoimmunity-predisposing genes. This view offers an explanation for comorbid conditions within individuals or within families. For example, cases of insulin-dependent diabetes mellitus (IDDM), Hashimoto's thyroiditis, and juvenile arthritis have been detected among family members of RA patients.

Importantly, incomplete disease concordance between identical twins calls for additional factors belonging to environment. They may even be responsible for sex discrepancy of autoimmune patterns. Sibling pairs proved to be limited in the small insufficient collections of homozygous and heterozygous pairs, and in the

small numbers of genetic and serological markers. In fact, each individual entity results from several combinations of genes (not always the same for a given disease) and external agents (also not always the same for a given disease).

These interactions include health-related quality of life. Supplemental risk factors are psychosocial trauma. Most projects in this field are based on the use of 36-item short form, and patients function at levels below those of the controls. A number of investigators have focused on diet, measuring consumption of coffee, tea, oil-rich fishes and alcohol. Given the number of anecdotal cases, it is not surprising that special attention has also been paid to exposures to silica and organic solvents now thought to trigger or to accelerate systemic scleroderma (SSc). Interestingly, this disease has been noticed to occur in patients living close to an airport (Shoenfeld, personal communication). In fact, there is increasing epidemiological evidence supporting the hypotheses that occupational silica exposure is associated with a variety of other systemic AD including SSc, RA, SLE and even non-SLE-driven glomerulonephritis and small vessel vasculitis [38]. Smoking is also discussed to be a risk factor for connective tissue diseases, among which are RA and SLE [39]. Curiously enough, several surveys in polluted sites brought the conclusions that sociological approaches are compulsory in such contexts.

With regard to the external components, silicone-breast implants have been unexpectedly shown to be instrumental in the occurrence of SSc and mixed connective tissue disease [40]. Once again, large population-based studies have been prompted by original case reports.

6. Gender

An outstanding risk factor for SLE, RA and pSS is gender. This term “female predominance” refers non only to sex differences of incidence, but also to variations in the severity. In all the human studies, 90% of SLE, RA and pSS patients are women, and in most of the autoimmunity-prone, the females get worse than the males. In fact, several illnesses similar to rheumatic diseases are not characterized by sexual dimorphism, nor by evident autoimmunity, yet the populations affected have the same hormonal background. There is, however, every likelihood that estrogenic exposures predate the incidence of this disorder. Though less common than in women, when it does occur in men, SLE tends to run a more severe course. It stands to reason that it has never to do with estrogens. Rather, in such cases the protective effect of testosterone has been bypassed by either endocrinopathies or genetic anomalies [41].

7. Infectious agents

Indisputably, immune attack on infectious agents is a health-maintaining response. Nonetheless, viral, bacterial and parasite infections play a part in autoimmune scenarios [42]. In this respect, instead of polyclonal activation, abnormal expression of micro-RNAs and molecular mimicry are suspected to operate. This model is based on the sharing of epitopes on proteins from unrelated species. However, we cannot predict which end-up peptides will be exposed by antigen-presenting cells and, therefore, which is the ultimate peptide shared by these two partners. Multiple experimental models of infection-induced ADs have been reported (Table 2). For example, myocarditis can be induced in susceptible mice by infection with cardiophilic coxsackievirus. Herpesvirus infection, in particular Epstein–Barr virus (EBV) infection, has been implicated in several major autoimmune conditions, including RA, SLE, pSS and multiple sclerosis (MS). In fact, EBV could simply contribute bystander effects by amplification of innate immune responses. Ironically, male and female mice are equally affected by SLE in germ-free environment.

Table 2
Examples of infection-related autoimmune diseases.

Disease	Infections agents
Rheumatoid arthritis	Epstein–Barr virus (EBV) Parvo B19 Chronic hepatitis C virus (HCHC)
Multiple sclerosis	EBV <i>Chlamydomphila pneumoniae</i>
Type-1 diabetes	Coxsackie virus B (Cox B) Cytomegalovirus Mumps
Sjögren's syndrome	Cox B EBV HCHC

Furthermore, the autoimmunity-inducing effects of infectious injuries do not square up with temporal changes in incidence of these diseases. Some of them, most notably MS and IDDM, have dramatically risen in the developed world, thus correlating inversely with the prevalence of infectious diseases that has reciprocally diminished. In contrast to IDDM and MS, RA seems to have declined over the same period of time. As a whole, this meaningful clinical and experimental observation is designated the “hygiene hypothesis” [43]. Infection might thus have historically prevented the development of ADs. This interpretation has fueled the idea of a North–South gradient in the prevalence of AD, with a reciprocal South–North gradient for infectious diseases. In line with these gradients, it is interesting that MS has emerged in West Indies in the population that had previously settled in Europe and returned back home, possibly to a drastic reduction in exposure to sunlight and intestinal parasites during childhood [44].

Differences in risk of specific ADs among countries have been refined recently. Thyroid disorders decrease progressively with the continuous iodine intake. However, given that the epidemiological procedures must be comparable, caution must be exercised in relying on these conclusions before completing meta-analyses.

Do we still believe in the hygiene hypothesis? Epidemiological, clinical and animal studies, taken together, suggest that broad exposure to a wealth of commensal, non-pathogenic micro-organisms early in life is associated with protection against some ADs. Most studies have, however shown, that SLE, RA or APS manifest themselves following infection. This contrasts with facilitation of the autoimmune process by limited exposure to infectious agents.

Clearly, whatever is the reason of this marked discrepancy, there is an increasing concern by epidemiology, so that we must admit that genetics and environment are both involved. The major challenge emerging is to develop a robust predictive model for autoimmunity onset. New insights into the pathogenesis of ADs may help identify the factors to be further analyzed. Recent evidence has indicated that environmentally-induced changes modify some forms of diseases. This novel and important process, referred to as epigenetics is a steadily growing research area [45]. Repertoire analyses in family members of patients with ADs illustrate how inheritance and somatic processes interplay to produce autoreactive Abs, and how relationships between environment and genotype connect their association to phenotype and disease. The association seems to be key in the geoepidemiology of ADs.

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References

- [1] Sanchez-Pernaute O, Ospelt C, Neidhart M, Gay S. Epigenetic clues to rheumatoid arthritis. *J Autoimmun* 2008;30:12–20.
- [2] Abraham M, Karni A, Dembinsky A, Miller A, Gandhi R, Anderson D, et al. In vitro induction of regulatory T cells by anti-CD3 antibody in humans. *J Autoimmun* 2008;30:21–8.
- [3] Deane S, Meyers FJ, Gershwin ME. On reversing the persistence of memory: hematopoietic stem cell transplant for autoimmune disease in the first ten years. *J Autoimmun* 2008;30:180–96.
- [4] Ikehara S. A novel method of bone marrow transplantation (BMT) for intracetable autoimmune diseases. *J Autoimmun* 2008;30:108–15.
- [5] Cervera R. Lessons from the “Euro-Phospholipid” project. *Autoimmun Rev* 2008;7:174–8.
- [6] Hughes GR. Hughes Syndrome (the antiphospholipid syndrome): ten clinical lessons. *Autoimmun Rev* 2008;7:262–6.
- [7] Doria A, Sarzi-Puttini P, Shoenfeld Y. Infections, rheumatism and autoimmunity: the conflicting relationship between humans and their environment. *Autoimmun Rev* 2008;8:1–4.
- [8] Frazer IH. Autoimmunity and persistent viral infection: two sides of the same coin? *J Autoimmun* 2008;31:216–8.
- [9] Matsuura E, Kobayashi K, Lopez LR. Preventing autoimmune and infection triggered atherosclerosis for an enduring healthful lifestyle. *Autoimmun Rev* 2008;7:214–22.
- [10] Sagi L, Sherer Y, Trau H, Shoenfeld Y. Pemphigus and infectious agents. *Autoimmun Rev* 2008;8:33–5.
- [11] Agmon-Levin N, Ram M, Barzilai O, Porat-Katz BS, Parikman R, Selmi C, et al. Prevalence of hepatitis C serum antibody in autoimmune diseases. *J Autoimmun* 2009;32:261–6.
- [12] Antonelli A, Ferri C, Ferrari SM, Colaci M, Fallahi P. Immunopathogenesis of HCV-related endocrine manifestations in chronic hepatitis and mixed cryoglobulinemia. *Autoimmun Rev* 2008;8:18–23.
- [13] Harrison LC, Honeyman MC, Morahan G, Wentworth JM, Elkassaby S, Colman PG, et al. Type 1 diabetes: lessons for other autoimmune diseases? *J Autoimmun* 2008;31:306–10.
- [14] Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Goncalves O, et al. Behcet's disease – a contemporary review. *J Autoimmun* 2009;32:178–88.
- [15] Mackay IR, Leskovsek NV, Rose NR. Cell damage and autoimmunity: a critical appraisal. *J Autoimmun* 2008;30:5–11.
- [16] Shoenfeld Y, Selmi C, Zimlichman E, Gershwin ME. The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity. *J Autoimmun* 2008;31:325–30.
- [17] Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003;2:119–25.
- [18] Xiang YJ, Dai SM. Prevalence of rheumatic diseases and disability in China. *Rheumatol Int* 2009;29:481–90.
- [19] Detels R. Epidemiology is an art: speech given at the ACE Abraham Lilienfeld Award ceremony, Tucson, Arizona September 16, 2008. *Ann Epidemiol* 2009;19S:286–7.
- [20] Lilienfeld D, Stolley P. Foundations of epidemiology. 3rd. New York, Oxford: Oxford University Press; 1994.
- [21] Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84:223–43.
- [22] Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1–9.
- [23] Binard A, Devauchelle-Pensec V, Fautrel B, Jousse S, Youinou P, Saraux A. Epidemiology of Sjogren's syndrome: where are we now? *Clin Exp Rheumatol* 2007;25:1–4.
- [24] Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *J Autoimmun* 2009;33:197–207.
- [25] Abu-Mouch S, Selmi C, Benson GD, Kenny TP, Invernizzi P, Zuin M, et al. Geographic clusters of primary biliary cirrhosis. *Clin Dev Immunol* 2003;10:127–31.
- [26] Hopkinson ND, Doherty M, Powell RJ. Clinical features and race-specific incidence/prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. *Ann Rheum Dis* 1994;53:675–80.
- [27] Aho K, Heliovaara M, Maatela J, Tuomi T, Palosuo T. Rheumatoid factors antedating clinical rheumatoid arthritis. *J Rheumatol* 1991;18:1282–4.
- [28] Aruckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1526–33.
- [29] McClain MT, Aruckle MR, Heinlen LD, Dennis GJ, Roebuck J, Rubertone MV, et al. The prevalence, onset, and clinical significance of antiphospholipid antibodies prior to diagnosis of systemic lupus erythematosus. *Arthritis Rheum* 2004;50:1226–32.
- [30] Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the

- symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004;50:380–6.
- [31] Shoenfeld Y, Blank M, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, et al. The mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune diseases – 2008. *Isr Med Assoc J* 2008;10:13–9.
- [32] Shoenfeld Y, Gilburd B, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, et al. The mosaic of autoimmunity: genetic factors involved in autoimmune diseases – 2008. *Isr Med Assoc J* 2008;10:3–7.
- [33] Johnson AE, Cavalcanti FS, Gordon C, Nived O, Palmer RG, Sturfelt G, et al. Cross-sectional analysis of the differences between patients with systemic lupus erythematosus in England, Brazil and Sweden. *Lupus* 1994;3:501–6.
- [34] Criswell LA, Amos CI. Update on genetic risk factors for systemic lupus erythematosus and rheumatoid arthritis. *Curr Opin Rheumatol* 2000;12:85–90.
- [35] Costenbader KH, Chang SC, Laden F, Puett R, Karlson EW. Geographic variation in rheumatoid arthritis incidence among women in the United States. *Arch Intern Med* 2008;168:1664–70.
- [36] Lahita RG. Predisposing factors to autoimmune disease. *Int J Fertil Womens Med* 1997;42:115–9.
- [37] Roben P, Barbas SM, Sandoval L, Lecerf JM, Stollar BD, Solomon A, et al. Repertoire cloning of lupus anti-DNA autoantibodies. *J Clin Invest* 1996;98:2827–37.
- [38] Brown JM, Pfau JC, Pershouse MA, Holian A. Silica, apoptosis, and autoimmunity. *J Immunotoxicol* 2005;1:177–87.
- [39] Gallego H, Crutchfield 3rd CE, Lewis EJ, Gallego HJ. Report of an association between discoid lupus erythematosus and smoking. *Cutis* 1999;63:231–4.
- [40] Brown SL, Langone JJ, Brinton LA. Silicone breast implants and autoimmune disease. *J Am Med Womens Assoc* 1998;53:21–4.
- [41] Shoenfeld Y, Zandman-Goddard G, Stojanovich L, Cutolo M, Amital H, Levy Y, et al. The mosaic of autoimmunity: hormonal and environmental factors involved in autoimmune diseases – 2008. *Isr Med Assoc J* 2008;10:8–12.
- [42] Pordeus V, Szyper-Kravitz M, Levy RA, Vaz NM, Shoenfeld Y. Infections and autoimmunity: a panorama. *Clin Rev Allergy Immunol* 2008;34:283–99.
- [43] Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity – friends or foes? *Trends Immunol* 2009;30:409–14.
- [44] Cabre P. Migration and multiple sclerosis: the French West Indies experience. *J Neurol Sci* 2007;262:117–21.
- [45] Trenkmann M, Brock M, Ospelt C, Gay S. Epigenetics in rheumatoid arthritis. *Clin Rev Allergy Immunol*; 2009.

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