Clinic Rev Allerg Immunol (2008) 34:283–299
DOI 10.1007/s12016-007-8048-8

# Infections and Autoimmunity: A Panorama

**V. Pordeus · M. Szyper-Kravitz · R. A. Levy · N. M. Vaz · Y. Shoenfeld**

Published online: 30 January 2008


**Abstract** For more than 2,000 years, it was thought that malignant spirits caused diseases. By the end of nineteenth century, these beliefs were displaced by more modern concepts of disease, namely, the formulation of the "germ theory," which asserted that bacteria or other microorganisms caused disease. With the emergence of chronic degenerative and of autoimmune diseases in the last century, the causative role of microorganisms has been intensely debated; however, no clear explanatory models have been achieved. In this review, we examine the current available literature regarding the relationships between infections and 16 autoimmune diseases. We critically analyzed clinical, serological, and molecular associations, and reviewed experimental models of induction of and, alternatively, protection from autoimmune diseases by infection. After reviewing several studies and reports, a clinical and experimental pattern emerges: Chronic and multiple infections with viruses, such as Epstein–Barr virus and cytomegalovirus, and bacteria, such as *H. pylori*, may, in susceptible individuals, play a role in the evolvement of autoimmune diseases. As the vast majority of infections pertain to our resident microbiota and endogenous retroviruses and healthy carriage of infections is the rule, we propose to focus on understanding the mechanisms of this healthy carrier state and what changes its configurations to infectious syndromes, to the restoration of health, or to the sustaining of illness into a chronic state and/or autoimmune disease. It seems that in the development of this healthy carriage state, the infection or colonization in early stages of ontogenesis with key microorganisms, also called 'old friends' (lactobacilli, bifidobacteria among others), are important for the healthy living and for the protection from infectious and autoimmune syndromes.

**Keywords** Infections · Autoimmune diseases · Chronic infection · Multiple infections · Old friends · Healthy carriage

This study was supported by the Wilhelm Agricola Research Grant, Federico Foundation, Zurich, Switzerland.

V. Pordeus
Clinical Research,
Pro Cardiaco Hospital Research Center—PROCEP,
Rio de Janeiro, Brazil

R. A. Levy
Rheumatology Discipline, Faculty of Medicine,
Universidade do Estado do Rio de Janeiro,
Rio de Janeiro, RJ, Brazil

N. M. Vaz
Department of Immunology and Biochemistry–ICB,
Universidade Federal de Minas Gerais,
Belo Horizonte, Brazil

V. Pordeus · M. Szyper-Kravitz · Y. Shoenfeld (✉)
Center for Autoimmune diseases, Department of Medicine B,
Sheba Medical Center,
Tel Hashomer, Israel
e-mail: shoenfel@post.tau.ac.il

## Introduction

For more than 2,000 years, physicians believed that all diseases were caused by *dyscrasia*, i.e., the imbalance of body humors (blood, phlegm, black, and yellow bile). This medical belief dominated the medical thinking until the nineteenth century [1] when it was challenged by Rudolf Virchow's cellular pathology, which stated that diseases derived from perturbations in cellular behavior. Later on, Louis Pasteur's proposal of the *germ theory* and Robert Koch's postulates lead the medical and scientific communities to accept the infectious origin of diseases. This

heralded a new period in medicine and biology: Hundreds of new diseases were described, and new techniques for diagnosis and treatment were developed. In parallel, the phenomena of immunity (capacity to resist infections) started to be systematically studied, hence, giving birth to immunology. With the introduction of basic sanitary systems and antibiotics, infection mortality decreased, and chronic degenerative diseases, namely, atherosclerosis, cancer, and autoimmune diseases, emerged as the leading cause of morbidity and mortality (at least in the Western world) [2]. These diseases have an inflammatory/immune basis, and the distinction of infectious diseases from inflammatory or autoimmune diseases is not clear-cut.

It is well recognized that viral, bacterial, and parasite infections may be involved in the arousal, flare, and on the other hand, in the prevention of autoimmune diseases [3]. The purpose of this review is to examine the state-of-the-art research on the relationship between infections and autoimmune diseases. Herein, we examine clinical, serological, and molecular associations between infection and autoimmune diseases. In addition, we review experimental models developed for the induction and protection from autoimmunity by infections.

## Rheumatoid Arthritis

### Clinical Associations with Infections

The occurrence of rheumatoid arthritis (RA) has been associated with several infections, among them are Epstein–Barr virus (EBV), Parvo B19, and chronic hepatitis C [4, 5]. In earlier studies, patients with RA exhibited increased titers of anti-EBV nuclear antigen 2 antibodies and increased frequency of circulating EBV-infected B cells compared to the healthy controls [5]. More recently, they also have been shown to have a tenfold increase in EBV DNA load [6]. Several similarities exist between RA and Parvo B19 infection: Both states are characterized by a chronic course, morning stiffness, joint deformation and destruction, rheumatoid nodules, as well as by the induction of rheumatoid factor (RF) and of cytokines such as interleukin-6 (IL-6) and transforming growth factor-α (TGF-α). Cases have been reported of RA development after acute Parvo B19 infection and of persistence of B19 RNA and of the VP-1 antigen in the synovial tissue of RA patients [7]. In a study on bone marrow samples from RA patients, 26% were positive for parvovirus B19, as compared to 4% in an historical control group of bone marrow [8]. Regarding bacterial infections, RA has been consistently associated with high titers of antibodies against *Proteus mirabilis* [9]. In a prospective study of 246 patients with recently diagnosed inflammatory arthritis, and followed for 1 year, patients' sera was tested against a panel of microorganisms (*Proteus mirabilis*, *Escherichia coli*, *Chlamydia trachomatis*, *Salmonella typhi*, *Shigella fexneri*, *Campylobacer jejune*, *Yersinia enterocolitica*, and *parvovirus B19*). Almost half of the patients fulfilled the American College of Rheumatology criteria for RA, 17% fulfilled the European Spondyloarthropathy Study Group (ESSG) criteria for a spondyloarthropathy, and 37% had undifferentiated arthritis. IgM and IgA anti-*Proteus mirabilis* antibodies were significantly higher in patients positive for the RF, compared with all other patients groups ($P<0.0005$ and 0.005). In addition, anti-*E. coli* IgM antibodies were also elevated in RF-positive RA patients, suggesting a role for *P. mirabilis* and *E. coli* infection in early seropositive RA [10].

### Experimental Models of Induction by Infection

SKG mice spontaneously develop T cell-mediated chronic autoimmune arthritis together with the production of several autoantibodies including RF and extra-articular lesions. These mice fail to develop arthritis in a microbially clean environment. However, a single intraperitoneal injection of zymosan, a crude yeast cell wall extract, can provoke severe arthritis, and β-glucans, which are the main constituents of zymosan, are responsible for the arthritogenic effect. Blockade of the major β-glucan receptor is able to prevent SKG arthritis triggered by β-glucans, and antibiotic treatment of fungi can prevent SKG arthritis in an arthritis-prone microbial environment [11].

The effect of microbial dose on collagen-induced arthritis (CIA) has been demonstrated regarding *Mycobacterium tuberculosis*. CIA can be induced even in CIA-resistant H-2(b) background of C57BL/6 mice when these mice are immunized with CII emulsified in CFA containing a high but not low dose of *M. tuberculosis* [12]. This high dose of *M. tuberculosis* seems to be required for maturation of dendritic cells enough to prime CD4+ helper T cells specific to CII antigen in draining lymph nodes of H-2b background of C57BL/6 mice. Using *Mycobacterium avium* intradermal injection to induce arthritis, researchers have characterized the importance of the chemokine receptor 2 (CCR2) in the arthritis-prone DBA1/j CCR2-null mouse. This strain has increased susceptibility to autoimmune arthritis induced by immunization with collagen type II (CII) and complete Freund's adjuvant (CFA). After intradermal infection with *M. avium*, a similar arthritis phenotype was detected in CCR2-null mice in the DBA/1j but not in the BALB/c background. These findings demonstrate that the CCR2-null state in an arthritic-prone genetic background leads to increased arthritis susceptibility after infectious (*M. avium*) and noninfectious (CII/CFA) challenges [13]. In an in vitro study on the effects of

*Helicobacter pylori* antigens on B lymphocytes cultures, autoantibodies, such as IgM RF, anti-single-stranded DNA and anti-phosphatidylcholine antibodies, were detected in the cultures' supernatant after the stimulation with *H. pylori* urease [14]. Thus, it seems that certain bacteria and fungi can activate arthritogenic T cells and evoke autoimmune arthritis in individuals who are genetically prone to produce arthritogenic autoimmune T cells.

### Experimental Models of Protection by Infection

In a recent study on experimental arthritis, the administration of a helminth extract prevented the development of inflammatory cell infiltration. This extract protected against the cartilage damage in the zymosan–arthritis model [15]. In another study, the oral administration of the viable bacterium *Lactobacillus casei* strain Shirota (LcS) to DBA/1 mice reduced the incidence and the development of CII-induced arthritis and reduced the levels of specific antibodies to CII in serum compared with the control mice [16]. The administration of LcS also inhibited delayed-type hypersensitivity response to CII in DBA/1 mice immunized with CII and CFA and suppressed the CII-specific secretion of interferon-gamma (INF-$\gamma$) from splenocytes ex vivo. These results suggest that the oral administration of LcS is able to modify the humoral and cellular immune responses to CII, and these modifications could result in the reduction of the development of CIA in DBA/1 mice.

Interestingly, the tolerogenic epitope of type II collagen (CII) is structurally mimicked by an epitope within the platelet aggregation-associated protein (PAAP) on *Streptococcus sanguis*. Feeding *S. sanguis* to DBA/1J pups delayed the onset of arthritis and reduced the rate, final severity, and percentage of affected limbs [17]. T cells primed with the tolerogenic epitope of CII proliferated more when incubated with PAAP(+) *S. sanguis* than with PAAP(−) *S. gordonii* or CII, suggesting an antigen-specific transmucosal tolerogenic effect. Therefore, in neonatal mice, bacterial surface antigens that mimic self can transmucosally stimulate antigen-specific inhibitory T cells. In adult mice immunized with CII, these antigen-specific inhibitory T cells manifest later as attenuated arthritis. The PAAP(+) *S. sanguis* appear to activate adult memory type II collagen-specific T cells, suggesting that systemic challenge with commensal self-mimicking microorganisms may perpetuate existing autoimmunity.

### Vaccination

The inoculation of live attenuated vaccines has been associated with reactive arthritis and with RA in several reports. In systematic reviews, new onset or relapse of RA, reactive, and chronic arthritis have been associated with the following vaccines: hepatitis B, miniature mass radiography (MMR; predominantly rubella vaccination), tetanus, typhoid/parathyphoid, influenza, polio, varicella, bacillus Calmette–Guerin (BCG), DTP (diphtheria, tetanus, and pertussis), and anthrax [18–22].

Transient arthralgia, acute arthritis, and chronic arthritis have been well recognized since the introduction of the rubella vaccine in the late 1960s. Risk factors associated with these effects were female gender, older age, and possibly some HLA types. However, more recent studies failed to demonstrate an increased risk for chronic arthropathy after rubella vaccination [18]

## Multiple Sclerosis

### Clinical Associations with Infections

Epidemiological studies have shown a significant higher prevalence of anti-EBV antibodies (100 vs 80–95%) and higher titers of anti-EBV viral capsid and anti-EBV nuclear antigen-1 (EBNA-1) antibodies among MS patients compared to the controls [6]. In a more recent systematic review of case control studies comparing EBV seropositivity and the risk for MS, an odds ratio of 13.5 was found [6]. In two recent large-cohorts' retrospective studies, the strongest predictors of MS were serum levels of IgG antibodies to EBNA complex or EBNA-1 [23, 24]. Among individuals who later developed MS, serum antibody titers to EBNA complex were similar to those of controls before the age of 20 years, but two- to threefold higher at age 25 years and older. The risk of MS increased according to the antibody titers; the relative risk was 9.4 in persons with high EBNA complex titers as compared to those with low titers. In longitudinal analyses, a fourfold increase in anti-EBNA complex or anti-EBNA-1 titers during the follow-up was associated with a threefold increase in MS risk. These results suggest an age-dependent relationship between EBV infection and development of MS [24]. Additional works suggest that early-in-life infection with EBV, usually oligo or asymptomatic, has a protective effect as oppose to later-in-life infection, which is associated with an increased risk for the development of MS [25]. Earlier studies demonstrated that MS patients have defective T-cell control of EBV-infected B cells [6]. A more recent study showed an increased frequency of CD8+ T cells responding to two immunodominant EBV epitopes. In addition, the authors characterized T cell cross reactivity between EBV antigens and the myelin basic protein [6]. The higher titers of measles antibodies in MS patients raised the concern of a possible causal association. However, this concern abated after the introduction of the measles vaccine, which was followed by a sharp drop in the incidence of measles not

accompanied by a significant change in the incidence of MS [18].

In a recent meta-analysis, MS patients were found more likely to exhibit *Chlamydophila pneumomiae* (Cpn) DNA in cerebrospinal fluid (CSF); however, no serological association was found both for the sera and the CSF with antibodies against Cpn [26]. A provocative hypothesis on the association of malaria with the development of MS has been presented. It proposes that comparing the old map of malaria with the later distribution of MS (in USA and Europe) supports the assumption that an early infection with *Plasmodium* sp. in childhood prevents later MS disease, whereas a silent infection at the time of adolescence or later might be responsible for the development of MS [27].

### Experimental Models of Induction by Infection

The classical model for multiple sclerosis inducted by the Theiler's murine encephalomyelitis virus (TMEV) infection has recently been related to the upregulation of a particular chemokine (CXCL2) during this infection [28]. Using a transgenic TMEV coding a *Haemophilus influenza* peptide, which mimics myelin proteolipid protein (PLP), the authors showed a rapid-onset demyelinating disease in mice. The authors also showed the importance of second signals, such as virus-activated molecules, as the molecular mimicry induced disease only in the TMEV infection context and did not induce disease when PLP was administered with CFA [29]. In another recent work, researchers have shown that the prior well-resolved infection with lymphocytic choriomeningitis virus (LMCV) during the neonatal period, predisposes adult mice to severe encephalomyelitis caused by a second infection with the same virus, a mechanism proposed as viral "déjà vu" [30]. In addition, transgenic animal models with the "insertion" of certain viral protein products have also been associated with the induction of multiple sclerosis [31]. Examining mimics of MS-related encephalitogenic peptides in all known human bacterial and viral peptides, homologies have been found in several organisms, predominantly in nonpathogenic gut bacteria. These suggest that the microorganism responsible for autoimmune activity in MS might be a normally occurring gut bacterium [32].

### Experimental Models of Protection by Infection

Comparing two mouse strains, one susceptible and the other resistant to encephalitis induced by infection with TMEV, it has been shown that CD4+ T cell numbers and reactivity to the virus capside peptide, were higher in the resistant strain, revealing the role of T CD4 cells in the viral clearance and protection from demyelinating disease [33]. Viral infection can prime T cells specific for central nervous system (CNS) antigens either through molecular mimicry with CNS proteins or through cytokine responses and bystander activation. In a murine model, mice infected with vaccinia virus encoding myelin protein developed clinical disease only after immune activation either with an unrelated virus such as murine cytomegalovirus or CFA, as opposed to challenge with LMCV, which suppressed autoimmunity [34]. In another murine model, an oral vaccine against diarrhea bacteria was capable of protecting mice from the establishment of experimental allergic encephalomyelitis (EAE) because of immunization with PLP peptide. The protection from disease was accompanied by increases in IL-4, IL-13, and IL-10 in lymphocytes culture supernatant, whereas a decrease in INF-$\gamma$ secreting cells was demonstrated in the nonvaccinated mice [35]. Interestingly, amelioration of EAE has been reported after experimental infection with *M. bovis* strain BCG [36].

### Vaccination

The association of MS and hepatitis B vaccination was first reported in France after the introduction of the recombinant vaccine. MS developed in 35 women who were later found to overrepresent the HLA-DR2 antigen and to have a strong family history of MS. More recently, in three large-scale case control studies, no evidence for HBV vaccination on the development of MS was found [18].

## Type 1 Diabetes Mellitus

### Clinical Associations with Infections

Several viruses have been proposed to be associated with type 1 diabetes mellitus (T1DM) such as rubella, coxsackievirus B (Cox B) [37], rota, mumps, and cytomegalovirus (CMV) [38]. Patients with congenital rubella syndrome have a high incidence of T1D (12–20%), and 50–80% exhibit anti-islet and anti-insulin antibodies, suggesting a possible role for the rubella virus in T1D. Cross-reactivity has been demonstrated between rubella capsid protein and extracts from human and rat pancreatic islets, and T cells from T1D cross-react with epitopes from rubella viral proteins and the β cell isoform of GAD [39]. Regarding the role of Cox B, epidemiological studies revealed conflicting results on the frequency of anti-Cox B antibodies in newly diagnosed T1D children as compared to nondiabetic controls [39] Several authors have isolated Cox B4 and Cox B5 viruses from the pancreas of patients with acute onset T1D, which could induce diabetes in susceptible mice, providing direct evidence for the involvement of Cox B infection in the development of T1D. Sequence homol-

ogy between P-2C, a noncapsid protein of Cox B4 virus and GAD (which is expressed by beta cells), has been described [39], and antibodies reacting to P-2C and GAD have been detected in T1D patients, providing a mechanism for Cox B4 involvement in the induction of T1D [39]. Despite the aforementioned data, other studies reported conflicting results, and no consensus has yet been achieved on the role of these infections on T1D [37]. Interestingly, children evaluated for multiple infections history (morbilli, parotitis, rubella, pertussis, or varicella) exhibited a higher risk for T1D [40].

### Experimental Models of Induction by Infection

In animal models, T1D can be induced by viruses either directly through the selective infection of pancreatic cells (rubella and Cox B4 viruses) or indirectly through autoimmune responses against β-cells elicited by viruses such as the Kilham rat virus. This last has been shown to activate macrophages to secrete inflammatory cytokines that up-regulate autoreactive CD8+ T cells and Th1 type CD4+ T cells, thereby, favoring autoimmunity [39]

Transgenic animal models with the insertion of certain viral protein products have been associated with the induction of T1DM [31]. In the NOD mice model, lymphocyte proliferation after lymphocyte loss (known as homeostatic proliferation), occurs as oligoclonal expansions, which are highly associated with disease. There is a well-known association of lymphopenia with autoimmune diseases and also with viral infections [41]. Using a transgenic mouse model of diabetes, which express lymphocytic choriomeningitis virus glycoprotein (LMCV-gp) in pancreatic beta cells and where the animals develop diabetes upon infection with LMCV or gp immunization, the authors characterized the importance of the affinity of TCR and its ligands, as well as the key role of a regulatory molecule, Cbl-b, in induction of T1DM, providing an interesting model to show that the multifactors are involved in overt experimental disease [42].

### Experimental Models of Protections by Infection

Several viruses, among them the LCMV and the mouse hepatitis virus, have been shown to protect against the development of T1D in susceptible rats (BB) and NOD mice [39]. A more complex relationship exists between T1DM and Coxsackie B4 (Cox B) infection. On the one hand, Cox B induces disease only if there is a prior level of insulitis. On the other hand, in the absence of this minimum threshold, it protects against diabetes [43]. Similarly, the encephalomyocarditis virus, which is diabetogenic in some mice strains, prevents T1D in NOD mice [39]. Prevention of T1D is postulated to involve induction of T-helper 2 immune responses or deletion of effector cells. Another example of protection from T1D by infection come from studies showing that activation of toll-like receptors through microbial elements protects NOD mice from diabetes, corroborating the hygiene hypothesis and suggesting a protective role of infections against autoimmune diseases [44]. Very recently, it was shown that the experimental infection with *Salmonella typhimurium* is able to prevent NOD mice from developing diabetes, even after the induction of the disease with cyclophosphamide [45]. A similar inhibitory effect was also demonstrated with helminth infection [46].

### Vaccination

The increasing incidence of T1D around the world raised the concern of a potential role for vaccination as an inciting event. Although one case-control study suggested that early vaccination with *Hemophylus influenza B* could be associated with an increased incidence of T1D, a large-scale cohort study that followed 10,000 Finnish children over a 10-year period, found no increased incidence and no vaccination–age association [18].

## Systemic Lupus Erythematosus

### Clinical Associations with Infections

Studies suggest that systemic lupus erythematosus (SLE) patients have unusual immune responses to EBV. Analyses of large cohorts of apparently healthy individuals have revealed that the development of SLE is preceded by abnormal antibody responses and the appearance of anti-Sm and anti-60 kD Ro autoantibodies years before clinical disease [47, 48]. These first lupus-specific autoantibodies arise from particular antibodies directed against EBNA-1. In addition, several recent papers have demonstrated increased viral load, increased numbers of latently infected peripheral B cells, impaired functional T cell responses, and association of the presence of EBV DNA in SLE patients compared with the controls [47–49]. Other authors reproduced similar finding, proposing other associations related to age, gender, anti-EBV immunoglobulin isotype, and CTLA-4 allelic variation [50]. Furthermore, a positive association has been demonstrated between levels of IgA anti-EBV antibodies and disease activity [51].

SLE and infectious mononucleosis patients exhibit the same patterns of immunoglobulin gene usage, with common oligoclonal B cells responses. After EBV infection, the expression of these B cell receptors is specifically censored, restoring equilibrium. The continuing high levels in SLE might arise from disordered regulation or chronic reactivation

of EBV [52]. Another current view is that normal immunity is perturbed by EBV infection and the generation of anti-EBNA-1 antibodies. Those particular anti-EBNA-1 antibodies that also bind lupus-specific autoantigens (Sm or Ro) are followed by the development of more complex autoimmune responses, culminating in clinical disease [47, 48].

Another notable association is the development of SLE in patients with HCV and Parvo B19 infection [7]. Attempts to associate parvovirus B19 to SLE have been frustrated [53]; however, acute infections with parvovirus 19 has been associated with disease flare-up [54, 55]. Several similarities can be found between the features of SLE and acute Parvo B19 infection, including malar rash, arthralgia and arthritis, fever, fatigue, lymphadenopathy, as well as serological markers. The chronic course of SLE as opposed to the self-limited presentation of parvo B10 infection distinguishes these two diseases. Regarding CMV, in a study of 22 female patients with SLE, evaluating the presence and quantity of human CMV genome, the authors found the virus genome in 100% of the patients, whereas it was present only in 73% of 15 healthy female controls ($p=0.02$) [56]. The cumulative evidence for a causal effect of infections on SLE remains to be proved, with the exception of the aforementioned extensive data regarding EBV. Experimental models of induction by infection

It was recently shown that the EBV latent membrane protein 2A, which effects development and activation of B cells, induces hypersensitivity of Toll-like receptor (TLR) stimulation in B cells. B cells are known bearers of TLRs, and this might suggest a mechanistic link between EBV infection and SLE [57]. A study showed that immunization with the structural CMV pp65 antigen, induced lupus-associated autoantibodies and severe glomerulonephritis [58].

### Experimental Models of Protection by Infection

One study reported that idiotypic-induced experimental lupus ameliorated the disease severity with the infection with BM5 murine leukemia virus (MuLV) [59]. This model explores the possible interaction between SLE and retroviral infection, as HIV infection has been cogitated to have a beneficial immunological impact over disease activity of SLE [59].

### Vaccination

Although the induction of experimental SLE has been reported in mice treated with pristane [60] and other hydrocarbon oil adjuvant used in vaccines [61], recent case control studies on SLE patients failed to demonstrate a role for HBV vaccination on disease development or for influenza vaccination on disease activity or antibody production [18].

## Atherosclerosis

### Clinical Associations with Infections

Atherosclerosis bears an inflammatory/immune basis and affects up to 20% of the developed world population. The first infection to be associated to atherosclerosis was *Chlamydophila pneumoniae* (formerly known as *Chlamydia pneumoniae*). In retrospective studies, a positive association was found between antibodies against this pathogen and documented atherosclerosis [62], but more recent meta-analysis have not confirmed it [63]. Similar conflicting results have been reported for the association with CMV [64]. One association that has been consistent in the literature is with periodontitis, which has an important infectious component. Certain periodontal microorganisms, such as *Campylobacter rectus* and *Peptostreptococcus micros*, are associated to higher degrees of carotid intima-medial wall thickness, an ultrasonographic measure of atherosclerosis [65]. *Porphyromonas gengivalis*, a prominent component of oral flora, has also been implicated in atherosclerosis (see below). Other microorganisms, such as *H. pylori*, herpes simplex virus, hepatitis A, mycoplasma, influenza virus, and other members of the herpes family have been associated to atherosclerosis but with weaker associations [66].

### Experimental Models of Induction by Infection

Molecular mimicry has been found between CMV proteins and with heat shock protein 60, an important antigen in the atherosclerotic process [67]. Accordingly, the experimental infection with murine cytomegalovirus (MCMV) and even after its inactivation aggravates atherosclerosis in a mouse model [68]. In line with the data linking periodontitis with atherosclerosis, *P. gingivalis* infection has been shown to accelerate atherosclerosis in Apo E null mice [69].

### Experimental Models of Protection by Infection

In line with more recent epidemiological data, experimental *Chlamydia pneumoniae* infection has not been shown to aggravate atherosclerosis in wild-type neither in Apo E null mice [70]. Similarly, pneumococcal immunization has been found to decrease atherosclerosis in a mouse model [71].

## Antiphospholipid Syndrome

### Clinical Associations with Infections

Antiphospholipid antibodies are clearly associated with several infections, ranging from viral, bacterial, and

parasitic infections. In a recent work, the main infections and agents associated to antiphospholipid syndrome (APS) were skin infection, representing 18% of the total; HIV (17%); pneumonia (14%); hepatitis C (13%); and urinary tract infection (10%)[63, 72]. Associations have also been reported between APS and chronic HCV infection [4], CMV [73], EBV [74], mycoplasma, pulmonary tuberculosis, malaria, *P. carinii*, and leptospirosis [3]. One work has showed the increased prevalence of anticardiolpin antibodies from the IgA isotype in patients with HTLV-1-associated spastic paraparesis [75].

In the APS, our group and others have demonstrated homology between β2 glycoprotein I (β2GPI) and several microbial proteins. After identifying relevant epitopes in the β2GPI molecule, our group searched homologies between these peptides and several microbial proteins in the Swiss Protein database, linking through molecular mimicry a wide range of infections and this autoimmune disease [76]. More recently, our group has shown the overlapping pattern of antibodies in the sera of rheumatic fever and APS patients, showing anti- β2GPI titers and functional activity in both groups of patients, as well as anti-protein M titers in APS patients, providing data-linking streptococcal-induced autoimmunity and the commonalities of APS and RF, like the heart valve and the CNS involvement [77].

Regarding the catastrophic antiphospholipid syndrome, infection as a triggering factor has been identified in up to 24% of patients [78], being an important cause of death in this subset of patients [79]. Although a clear relationship between anti-phospholipid antibodies and infections exists, no particular microorganism has been consistently found be involved in the disease pathogenesis.

### Experimental Models of Induction by Infection

Through immunization of mice with bacterial and viral peptides, which share homology with β2 domain, raised titers of anti-cardiolipin and anti-β2GPI have been documented [80].

### Experimental Models of Protection by Infection

To date, no study has been published demonstrating a protective role of infections on the APS.

## Polymyositis PM/Dermatomyositis

### Clinical Associations with Infections

As recently reviewed, PM is more consistently associated to parvovirus B19, HIV, and HTLV-1 [81]. In a cohort of chronic hepatitis C patients, the occurrence of inflammatory myopahty was in 2 out of 180 individuals [4]. Serological association with Cox virus (A7, B3, and B4) has been reported in PM and DM patients, raising concern to this agent in this group of diseases [82]. In a recent cohort study of juvenile DM, no significant serological or molecular correlations were demonstrated with parvovirus B19 [83].

### Experimental Models of Induction by Infection

The main experimental model of PM is the chronic inflammatory myositis induced by Coxs B1 Tucson, in which viral epitopes have recently been characterized [84]. In mice experimental infection with the Ross River virus is also able to induce arthritis and myositis [85]. The experimental infection with *Trypanosoma cruzi* induces myocarditis and myositis, and the multiple infections with different strains of this protozoan are able to exacerbate the inflammatory muscular disease [86].

### Experimental Models of Protection by Infection

To our best knowledge, no experimental models regarding protection of PM/DM by infection has been published.

### Vaccination

BCG vaccination has been associated to the development of dermatomyositis in three case reports [22].

## Systemic Sclerosis

### Clinical Associations with Infections

An increased occurrence of parvovirus B19 DNA in skin biopsy samples of systemic sclerosis (SSc) patients has been recently reported as compared to healthy controls, particularly for the gene component VP1, which was found in 75% of SSc patients against 53% [87]. Regarding EBV antibodies, no significant differences have been found between SSc patients and healthy individuals [5], as opposed to raised titers of antibodies to CMV matrix protein UL83CMV and to *H. pylori* found in the sera of SSc patients as compared to the controls [88, 89].

### Experimental Models of Induction by Infection

Using a library of random peptides and pooled IgG from 90 patients with diffuse and limited SSc, a peptide was identified that reacted with 93% of the IgG sera. Using a database of protein sequences, the authors observed a high homology of this peptide with autoantigens, such as ribonucleoprotein RNP, filarin, cytocrome C, and with the

protein UL94 from CMV [90]. Furthermore, the reacting antibodies induced apoptosis in human endothelial cells culture (HUVEC). Thus, a possible role for CMV infection is proposed in the induction of autoantibodies capable of inducing apoptosis of endothelial cells, at least in vitro, in SSc [90]. The mechanisms of endothelial cell damage regarding Ssc and atherosclerosis have been recently reviewed [67]. In mice, experimental *Mycoplasma hominis* infection is able to induce autoantibodies associated with SSc [91].

### Experimental Models of Protection by Infection

No experimental models have been published.

## Primary Vasculitis

Primary vasculitis (or vasculitides) is a heterogeneous group of diseases characterized by inflammation of the blood vessel wall, encompassing several disorders according to the size of the affected vessel: Takayasu's arteritis and giant cell arteritis (predominantly large vessels), Kawasaki syndrome and polyarteritis nodosa (PAN; predomominantly medium vessels), and Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome, Henoch–Schönlein purpura, essential cryoglobulinemia, and cutaneous leukocytoclastic angiitis (predominantly small vessels). Secondary vasculitis are associated with a wide range of viral (hepatitis C and B), bacterial (staphylococcus, ricketsia), fungal, and parasitic infections. The group of vasculitis with an unexplained etiology, which is believed to be autoimmune, is called primary, and its relationships with infections are our main interest. A excellent review on the subject have recently been published [92].

### Clinical Associations with Infections

A notable association is the infection by HCV in patients with mixed cryoglobulinemia and other vasculidities [4]. In a small series of 13 vasculitis patients, no significant serological correlations were found with parvovirus B19 and V9 erythrovirus [93]. Chlamydia pneumonia, parvovirus B19, and human herpes virus have been suggested to be associated to giant cell arteritis; however, this has not been reproduced [94]. To date, no specific pathogen has been proposed to explain Takayasu's arteritis pathophysiology. The first pathogen associated with PAN was hepatitis B virus. After the widespread availability of HBV vaccination, this association has substantially decreased. Besides HBV, HCV, and HIV have also been found in patients with PAN, and several reports suggest that certain bacterial infections, such as *Streptococcus* sp., *Klebsiella* sp, *Pseudomonas* sp., and *Yersinia* sp., may also be associated [92].

Regarding Wegener's granulomatosis, inconsistent associations with parvovirus B19, CMV, and in particular, with *S. aureus* have been reported [92]. Kawasaki disease has not been consistently associated to a particular infectious agent, although association have been reported with *Coxiella burnetti*, EBV, HIV, B19, varicella zoster virus(VZV), dengue virus, and *M. pneumoniae* [92]. Recently, a controversy regarding the novel human corona virus (HN-CoV) and Kawasaki disease is taking place in the literature [95]. Beçeht's disease exhibits the same scientific status of other primary vasculitis: no consistent associations, although the reported ones include, herpes simplex virus (HSV), HCV, B19, *S. sanguis, C. pneumoniae*, and HIV [92]. A quite long list of microorganisms has been associated to Henoch–Schönlein purpura, which comprises *Streptococcus* sp, *M. pneumoniae*, *Yersinia* sp., *Legionella*, *H. pylori*, HBV, HBV, VZV, adenovirus, CMV, B19, and M tuberculosis. Recentlty, *Bartonella hensea* have been serologically associated to this disease but without independent confirmation yet [96].

### Experimental Models of Induction by Infection

Transgenic mice deficient for INF-$\gamma$ or INF-$\gamma$ receptor, upon experimental infection with murine gamma-herpesvirus 68 (gammaHV68) after a latency period, develop large-cell vasculitis. The same authors characterized the importance of IFN-$\gamma$ in controlling the reactivation of the gamma-HV68 in mice [97]. In another model, the intraperitoneal injection of *Candida albicans* water soluble fraction prepared from *C. albicans* culture supernatant was able to induce coronary arteritis, a hallmark of Kawasaki disease, and has been related to complement activation by the lectin pathway [98]. In a model of the central nervous system, vasculitis induced by intrathecal injection of *Streptococcus pneumoniae* type 3 isolated from a patient with meningoencephalitis, it was shown that the deletion of TGF receptor II in polymorphonuclears favored bacterial clearance and prevents subsequent cerebral vasculitis [99]. Finally, LPS has recently been shown to aggravate destructive inflammation in a small vessel vasculitis (glomerulonephritis) model induced by anti-myeloperoxidase antibody [100].

### Experimental Models of Protection by Infection

To date, no experimental models characterizing a protective role of infections in vasculitis have been reported.

### Vaccination

In selected cases, vaccination with HBV, mumps, measles, influenza, and varicella has been associated to primary vasculitis [18].

## Sjögren's Syndrome

### Clinical Associations with Infections

Sjögren's syndrome (SSj) occurrence has been reported in chronic hepatitis patients [4]. Coxsackievirus' RNA was found in salivary biopsies of patients with SSj in increased frequency when compared to the healthy controls; however, this finding has not been confirmed by other authors [101]. Regarding EBV, SSj patients exhibit significantly higher titers of IgG to EBNA 2 compared to the healthy controls and are associated with pulmonary involvement [5].

### Experimental Models of Induction by Infection

Using a transgenic strain of B6-Lpr/lpr deficient for *fas* (CD95), and important protein in apoptosis induction, authors have shown that the infection with murine CMV induced a chronic sialadenitis resembling SSj [102]. Similarly, the infection of LP-BM5 murine leukemia virus, inducer of a murine severe immunodeficiency termed murine AIDS, is also able to generate a sialadenitis resembling SSj and also an exocrine pancreatitis, which might provide a model for evaluating the association between SSj and type 1 diabetes [103].

### Experimental Models of Protection by Infection

To our best knowledge, no experimental models have been reported regarding protection of SSj by infection.

## Autoimmune Thyroid Diseases

### Clinical Associations with Infections

The infection by *Yersinia enterocolitica* has been hypothesized to be linked to autoimmune thyroid diseases, both Graves' and Hashimoto's diseases [104]; however, conflicting data regarding the high prevalence of this infection in the healthy population weakens this hypothesis [105, 106]. The efforts to associate Graves' and Hashimoto's thyroiditis to retroviruses have generated conflicting data: They have been observed in chronic HCV infection and more consistently with IFN-α treatment [107]. Recent data point to a prominent role of IFN-α therapy in the induction of thyroid autoimmunity in association to HCV infection [108]. Also, subclinical hypothyroidism has been observed in individuals with HIV infection, particularly those under highly active retroviral therapy, but no thyroid autoimmunity has been detected in these patients [108].

### Experimental Models of Induction by Infection

An important role of both Th1 and Th2 cytokines has been demonstrated for the development of hyperthyroidism through infection with a transgenic adenovirus bearing thyroid-stimulating hormone (TSH) receptor, reviewing the notion that this disease might solely depend upon Th1 cytokines [109]. The same group has recently shown the importance of $CD25^{+}CD4^{+}$ regulatory T cells (Tregs) in this disease through depletion of Tregs caused enhancement of disease severity [110]. It has been shown that Hashimoto's thyroiditis exhibit thyrocytes with overexpressed Toll like receptor 3 (TLR3), an important receptor for pathogen associated molecular patterns (PAMPs) such as dsRNA. It has also been shown that infection with Influenza virus, a single strand RNA virus, is an activator of TLR3 dependent cascades in murine thyrocytes culture, linking the innate immune response observed in Hashimoto's thyroiditis and infectious stimuli like influenza A virus [111].

### Experimental Models of Protections by Infection

Schistosoma mansoni experimental infection protected mice from experimental Graves' disease induced by transgenic adenovirus bearing THS receptor [112].

## Myocarditis, Dilated Cardiomyopahty, and Chagas's Disease

One of the most studied cases of autoimmunity and parasitic infection is Chagas' disease chronic cardiomyopathy (CMP), in which infection by *T. cruzi* is believed to induce, through several mechanisms of inflammatory and autoimmune response, damage to the heart. This process in the long-term leads the infected patient to a syndrome of dilated CMP and heart failure provoked by antibodies and T cells directed toward heart proteins, which has been shown to share degrees of homology with *T. cruzi* proteins [113].

### Clinical Associations with Infections

Several infectious agents have been serologically and molecularly associated with myocarditis and dilated CMP, with a high variability of results according to the author. The microorganisms reported include parvovirus B19, Cox B, CMV, EBV, adenovirus, influenza, HBV, HCV, poliovirus, mumps, HIV, respiratory syncytial virus, varicella, streptococcus, tuberculosis, staphylococcus, toxoplasma, plasmodium, *B. burgdoferi*, syphilis, and leptospirosis [114]. More recently, an isolated case of a patient with myopericarditis and *Campylobacter* sp. enteritis has been reported [115].

### Experimental Models of Induction by Infection

Several mouse models demonstrate the role of Cox B3-inducing myocarditis [116], including transgenic animal models [117]. It has been shown that the stimulation of toll-like receptor 4 favors the overture of myocarditis induced by Cox B in a model where the transgenic expression of TGF-β in the pancreas initially protected mice from develop myocarditis, reinforcing the multiple steps in disease induction [118]. Also, the occurrence of myocarditis with the experimental infection with MCMV and encephalomyocarditis virus has been reported [119].

### Experimental Models of Protection by Infection

A number of studies show the protection from myocarditis induced by infection in experimental models through dissecting activation cascades with transgenic mice. However, to date, no models were found regarding the amelioration of myocarditis by infection.

### Vaccination

After smallpox vaccination, myopericarditid has been reported at an incidence of 7.8 cases per 100,000 in the 30 days after vaccination, a rate of 3.6% higher than the expected, suggesting a causal relationship [18].

## Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompass a group of diseases of autoimmune pathophysiology that includes mainly Crohn's disease (CD) and ulcerative colitis (UC). Both are associated with several infectious agents, and their development has been related to changes in the intestinal resident microflora.

### Clinical Associations with Infections

IBD has a marked geographic variation, with increased rates in high-socioeconomic-status individuals, who exhibit the lowest enteric infection rates, and an association with the highest rates of multiple sclerosis [120]. An association has been reported for *H. pylori*, with a particular form of CD, the ulcerative colitis-like form, through a PCR method, but a negative association was found with the other forms of CD [121]. Interestingly, IBD patients were found to have lower levels of antibodies against *H. pylori* in comparison to healthy matched controls [122]. In established CD and UC, after 6–13 years of follow-up, patients are seropositive for *Yersinia enterocolitica* infection [123]. Also, infection with *Mycobacterium avium paratuberculosis* (MAP) has been shown to occur at increased rates in patients with CD [124]. Very recently, molecular mimicry between MAP proteins and self-peptides has been characterized: Cross-reactivity between MAP proteins and a self-peptide gastrointestinal glutathion peroxidase has been reported in 30% of the evaluated patients, proposing a novel autoantigen in this disease [125]. Infection with other microorganisms such as *Clostridium difficile*, CMV, and *Entamoeba hystolitica* might also be associated with IBD [126]. Interestingly, it has been observed that appendectomy because of appendicitis (not incidental) decreases risk for UC, but it might increase the risk for the development of CD [126]. As recently reviewed, the manipulation of intestinal flora in patients with IBD through the administration of probiotics, i.e., Lactobacilli and Bifidobacteria among others, is a promising field with current clinical trials investigating it [127].

### Experimental Models of Induction by Infection

It has been shown that intestinal flora is a requirement for the development of IBD in IL-10 deficient mice, as germ-free counterpart mice are resistant to the disease. Interestingly, the monocolonization of given bacterial species is also not sufficient for the overture of enterocolitis [128].

### Experimental Models of Protection by Infection

The infection with *Schistosoma mansoni* or even the administration of its egg has a beneficial role in preventing the colitis provoked by direct intrarectal administration of tri/di-nitrobenzene sulphonic acid (DNBS) [129]; the same beneficial effect has been shown for tapeworm, *Hymenolepis diminuta*, in another experimental model of colitis induced by DNBS, and this effect was dependent on IL-10 [130]. Also, the oral administration of *Trichuris sui* ova to patients with UC was associated with no side effects and clinical efficacy [131]. Regarding probiotics, the administration of *Lactobacillus* and *Bifidobacterium* sp. was able to prevent the development of spontaneous colitis in IL-10-deficient mice [128].

## Autoimmune Thrombocytopenic Purpura ITP

### Clinical Associations with Infections

Several authors have suggested that persistent infections with HIV, HCV, and *H. pylori*, are associated with ITP, and several studies have demonstrated improvement of platelet counts with suppression or eradication of infection, suggesting a role of persistent antigen exposure to the pathogenesis of ITP [132]. In HIV-infected patients,

immune platelet destruction has been shown to be associated with the presence of a cross-reactive antibody, recognizing both the conformational structure of HIV-gp-120 and platelet gpIIIa (CD61) [132]. The role of *H. pylori* infection on the development or persistence of ITP and its eradication on platelet counts emerged from several small studies and from prospective clinical trials [133, 134]. Cross-reactivity between platelet-associated IgG and *H. pylori* Cag protein suggests that molecular mimicry may play a key role in the pathogenesis of a subset of ITP patients [132].

### Experimental Models of Induction by Infection

The experimental infection with lactate dehydrogenase-elevating virus in mice treated with monoclonal autoantibodies against platelet, in smaller doses than those to induce disease, was found to be the trigger for the development of severe thrombocytopenia. The authors further characterized the importance of phagocytosis and INF-$\gamma$ for the overture of this disease [135]. Recently, using a phage display library screening from antibodies against glycoprotein IIIa (autoantigen from platelets) of patients with HIV infection and thrombocytopenia, the authors showed that part of the peptides rescued by the antibodies from the phage display library shared a high homology with HIV-1 proteins, which also were shown to inhibit the anti-platelet antibody toxic effect to platelets in vitro [136].

### Experimental Models of Protection by Infection

No models have been published in this experimental scenario.

### Vaccination

Vaccination with HBV and MMR has been associated with ITP. Acute ITP developed shortly after MMR vaccination in 23 of ~700,000 Finnish children, which together with multiple case reports, led to the establishment of causality [18].

## Guillain–Barré Syndrome

### Clinical Associations with Infections

This polyradicular neuropathy has been associated in a more consistent way to *Campylobacter jejuni*, *Haemophilus influenza*, HIV, and CMV, and it has also been reported less strongly to EBV and *M. pneumoniae* [137]. Although the association between *C. jejuni* and Guillain–Barré Syndrome (GBS) has been well documented, the latest estimated incidence of GBS in patients with *C. jejuni* enteritis is 1.7:1,000, a rate 77 greater than for the general population [138]. The association between *GBS* and *H. pylori* infection has also been reported [139].

### Experimental Models of Induction by Infection

In susceptible mice, immunization with *Brucela melitensis* induced anti-gangliosides antibodies along with flaccid limb weakness. Importantly, these clinical and serological effects were enhanced when compared to mice immunized with *C. jejuni* [140]. In addition, *C. jejuni* specific genes for the glycosilation of lipo-oligosacharides have been shown to play an important role in the induction of anti-gangliosides antibodies through molecular mimicry. As the immunization with transgenic *C. jejuni* deficient for these genes generated smaller titers of anti-ganglioside antibodies and less weakness in mice, it characterized the importance of those bacterial structures in the induction of pathogenic antibodies [141].

### Experimental Models of Protection by Infection

To our best knowledge, no experimental models of protection by infection have been published to date.

### Vaccination

The association of influenza vaccination with GBS was documented after the mass inoculation in the USA with the "swine flu" A/New Jersey/8/76 vaccine in 1976–1977. Recipients of this specific vaccine had a relative risk of 7.6 for developing GBS, and an excess of nine cases per million was confirmed [18]. In a more recent study from the Vaccine Adverse Events Reporting System, which examined all cases of GBS between the years 1991–1999, the relative risk for GBS after influenza vaccination was 4.3 and, for severe GBS, 8.5, compared to adult tetanus–diphteria vaccine control group, suggesting a causal association [142]. Less strong is the case for the association of GBS and oral poliovaccine. A nationwide vaccination campaign in Finland was associated with a rise in GBS cases; however, some evidence suggested that the initial increase in cases preceded the campaign, and an additional study failed to support this association [18].

## Post-Streptococcal Syndromes: Rheumatic Fever and PANDAS

### Rheumatic Fever

The prototypical autoimmune disease induced by a bacterial infection is rheumatic heart disease (RHD), which occurs

approximately in 1.2% of children after oro-pharyngeal infection with β-hemolytic group A streptococci. Certain class I and II HLA haplotypes have been implicated in the pathogenesis of RHD, which has been shown to involve humoral and cellular immunological components [143]. Molecular mimicry has been proposed to be responsible for the pathogenesis of the disease, which also shows a degenerate pattern of TCR recognition, as T cell clones infiltrating the heart of patients also responded to M protein when subjected to lymphoproliferative tests [144]. In addition, RHD has been induced by immunization with the M protein from group A streptococci [145]. Interestingly, abrogation of the disease was achieved through intranasal administration of protein M epitopes [146].

### Pediatric Autoimmune Neuropsychiatric Disorders

Recently, a wide spectrum "pediatric autoimmune neuropsychiatric disorders" (PANDAS) has been described as associated with streptococcal infection that can present clinically from Tourette's syndrome to chorea. PANDAS is related, at least epidemiologically, to group A streptococci infection [147], and clearance of serum IgG through plasmapheresis and IVIG reposition has been associated with a remarkable clinical improvement of PANDAS [148]. Anti-basal ganglia antibodies are associated with this disease [149].

### The Global Picture

In the process of reviewing the literature on the association of infections and autoimmune diseases, a pattern of clinical associations emerges: chronic viral infections, such as EBV and CMV, and chronic bacterial infections, like *H. pylori*, are more frequently associated to multiple autoimmune diseases and, indeed, have experimental models confirming their association with induction of autoimmunity. More recently, the disease overture has been found to rely on multiple steps of induction, be it viral persistence, chronic infection of B cells, or viral deja vus.

Several mechanisms have been proposed for the role of infectious agents on the induction of autoimmune diseases. Molecular mimicry or structural homologies between infectious and host components, underlies the pathomechanism in rheumatic fever, where the M component of the streptococcus membrane share homologies with heart, brain, and joint synovium peptides. In susceptible individuals, this molecular mimicry modifies lymphocytes reactivity in a progressive and chronic fashion that ultimately lead to autoimmune disease. Molecular mimicry is considered a putative mechanism also in GBS, APS, and MS. Epitope spreading or the appearance of a new antibody or the T cell response to different epitopes on the same or on another antigen has been demonstrated in experimental models and human diseases. In SLE, authors demonstrated intermolecular spreading from Sm antigen to RNP reactivity, and in pre-clinical diabetes and in RA studies, intra- and intermolecular spreading has been observed [3]. In this context, infections could play an important role either through release of sequestered antigens after tissue damage or upregulation of the display of cryptic epitopes under the inflammatory conditions. Bystander activation is another proposed mechanism in which, under the immune milieu where priming of microbial antigen-specific T cell is taking place, potentially self-reactive T cells are activated. Priming of reactive T cells may occur through an additional mechanism. Infectious agents through tissue injury may cause the release of self antigens, which are processed and presented by antigen-presenting cells, leading to priming of self-reactive T cells. Also, superantigenic T cell activation by viral and bacterial products, which can cross-link the T cell receptor and MHC molecule independent of specific antigen recognition, may favor the induction of an autoimmune disease.

It is well known that viral infections commonly produce transient autoimmune responses (usually directed against blood cells), transient elevation in autoantibodies titers, and arthritis (Parvo B19, rubella). For the vast majority of patients, symptoms and antibody titers decline. Even in cases where the role of microorganisms is well defined, like in rheumatic fever and *Streptococcus pneumoniae* groups A, only about 1.2% of infected children actually develop rheumatic fever. Therefore, rather than focusing on the presence or absence of a microorganism in the context of an autoimmune disease, it is the complex immunopathological interaction between the organism and microorganisms, which is the most important factor for the development of an acute infection, for the restoration of health or for the development of a chronic state or an autoimmune disease. This interaction relies in a multitude of factors that include genetic, epigenetic, behavioral, and symbolic factors, as discussed in a recent published book [150].

Caution should be applied in the leap from experimental models of autoimmune disease induced by infections to clinical disease, as in the experimental models, illness occurs only in particular circumstances such as in susceptible strains, under particular environmental conditions, and with the usage of adjuvant molecules. Furthermore, the widespread genetic manipulation of animals and molecules are commonplace in these models. With the help of experimental models, eventually, genetic determinants and pathways are revealed, but often, other determinants remain unclear. It should be acknowledged that diabetes in NOD mice occurs in 90% of females maintained in specific pathogen-free environment and that it decreases to less than 5% in more conventional (dirtier) environments [41].

Regarding protection from autoimmune diseases by infections, it seems that the 'old friends,' i.e., helminthes, lactobacilli, bifidobacteria, and saprophytic bacteria from the resident flora, are associated with the inhibition of autoimmune diseases, both in experimental and clinical setting. At present, clinical trials are being conducted with these microorganisms.

The amount of data accumulated regarding infections and autoimmune diseases is vast and expanding. Maybe what is needed now is a clearer definition of an immunological physiology and, then, its pathological deviations. For that, we need a new conceptual framework with different approaches and tools that can already be seen in many areas of biology, collectively named 'system's biology.' Hence, we might reach a clearer understanding of the healthy organism, and its pathological deviations, like infections and autoimmune diseases. Specially, because, today, the concept of 'super-organism' arises from the deeper layers of biology, the fact that we are composed of bacteria and retroviruses, as evidenced from our genome and microbiome analysis, revealing that host and microorganisms are yoked into a chimera of sorts [151].

## References


1. Nutton V (2005) The fatal embrace: Galen and the history of ancient medicine. Sci Context 18:111–121
2. De Flora S, Quaglia A, Bennicelli C, Vercelli M (2005) The epidemiological revolution of the 20th century. FASEB J 19:892–897
3. Shoenfeld Y, Rose NR (2004) Infection and autoimmunity, 1st edn. Elsevier, Amsterdam
4. Ramos-Casals M, Jara LJ, Medina F et al (2005) Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC Registry): patterns of clinical and immunological expression in 180 cases. J Intern Med 257:549–557
5. Yamazaki M, Kitamura R, Kusano S et al (2005) Elevated immunoglobulin G antibodies to the proline-rich amino-terminal region of Epstein–Barr virus nuclear antigen-2 in sera from patients with systemic connective tissue diseases and from a subgroup of Sjogren's syndrome patients with pulmonary involvements. Clin Exp Immunol 139:558–568
6. Pender MP (2004) Epstein–Barr virus and autoimmunity. In: Shoenfeld Y, Rose NR (eds) Infection and autoimmunity. 1st edn. Elsevier, Amsterdam
7. Severin MC, Shoenfeld Y (2004) Parvovirus B19 infection and its association with autoimmune disease. In: Shoenfeld Y, Rose NR (eds) Infection and autoimmunity. 1st edn. Elsevier, Amsterdam
8. Lundqvist A, Isa A, Tolfvenstam T, Kvist G, Broliden K (2005) High frequency of parvovirus B19 DNA in bone marrow samples from rheumatic patients. J Clin Virol 33:71–74
9. Subair H, Tiwana H, Fielder M et al (1995) Elevation in anti-proteus antibodies in patients with rheumatoid arthritis from Bermuda and England. J Rheumatol 22:1825–1828
10. Newkirk MM, Goldbach-Mansky R, Senior BW, Klippel J, Schumacher HR Jr, El-Gabalawy HS (2005) Elevated levels of IgM and IgA antibodies to Proteus mirabilis and IgM antibodies to Escherichia coli are associated with early rheumatoid factor (RF)-positive rheumatoid arthritis. Rheumatology (Oxford, England) 44:1433–1441
11. Yoshitomi H, Sakaguchi N, Kobayashi K, Brown GD, Tagami T, Sakihama T, Hirota K, Tanaka S, Nomura T, Miki I, Gordon S, Akira S, Nakamura T, Sakaguchi S (2005) A role for fungal {beta}-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. JEM 201:949–960
12. Kai H, Shibuya K, Wang Y, Kameta H, Kameyama T, Tahara-Hanaoka S, Miyamoto A, Honda S, Matsumoto I, Koyama A, Sumida T, Shibuya A (2006) Critical role of M. tuberculosis for dendritic cell maturation to induce collagen-induced arthritis in H-2b background of C57BL/6 mice. Immunology 118:233–239
13. Quinones MP, Jimenez F, Martinez H et al (2006) CC chemokine receptor (CCR)-2 prevents arthritis development following infection by *Mycobacterium avium*. J Mol Med (Berlin, Germany) 84:503–512
14. Yamanishi S, Iizumi T, Watanabe E et al (2006) Implications for induction of autoimmunity via activation of B-1 cells by *Helicobacter pylori* urease. Infect Immun 74:248–256
15. Rocha F (2006) Protective role of helminthiasis in the development of autoimmune diseases. Clin Dev Immunol 13:159–162
16. Kato I, Endo-Tanaka K, Yokokura T (1998) Suppressive effects of the oral administration of Lactobacillus casei on type II collagen-induced arthritis in DBA/1 mice. Life Sci 63:635–644
17. Costalonga M, Hodges JS, Herzberg MC (2002) *Streptococcus sanguis* modulates type II collagen-induced arthritis in DBA/1J mice. J Immunol 169:2189–2195
18. Schattner A (2005) Cosequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines. Vaccine 23:3876–3886
19. Tishler M, Shoenfeld Y (2004) Vaccination may be associated with autoimmune diseases. IMAJ 6:430–432
20. Tinazzi E, Ficarra V, Simeoni S, Artibani W, Lunardi C (2006) Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. Rheumatol Int 26:481–488
21. Vasudev M, Zacharisen MC (2006) New onset rheumatoid arthritis after anthrax vaccination. Ann Allergy Asthma Immun 97:110–112
22. Shoenfeld Y, Aron-Maor A (2000) Vaccination and autoimmunity—'vaccinosis': a dangerous liaison? J Autoimmun 14:1–10
23. DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A (2006) Epstein-Barr virus and multiple sclerosis: evidence of association from a prospective study with long-term follow-up. Arch Neurol 63:839–844
24. Levin LI, Munger KL, Rubertone MV et al (2005) Temporal relationship between elevation of Epstein–Barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. J Am Med Assoc 293:2496–2500
25. Haahr S, Hollsberg P (2006) Multiple sclerosis is linked to Epstein–Barr virus infection. Rev Med Virol 16:297–310
26. Bagos PG, Nikolopoulos G, Ioannidis A (2006) Chlamydia pneumoniae infection and the risk of multiple sclerosis: a meta-analysis. Mult Scler (Houndmills, Basingstoke, England) 12:397–411
27. Kissler H (2001) Is multiple sclerosis caused by a silent infection with malarial parasites? A historico-epidemiological approach: part I. Med Hypotheses 57:280–291
28. Rubio N, Sanz-Rodriguez F, Lipton HL (2006) Theiler's virus induces the MIP-2 chemokine (CXCL2) in astrocytes from genetically susceptible but not from resistant mouse strains. Cell Immunol 239:31–40
29. Croxford JL, Olson JK, Anger HA, Miller SD (2005) Initiation and exacerbation of autoimmune demyelination of the central

nervous system via virus-induced molecular mimicry: implications for the pathogenesis of multiple sclerosis. J Virol 79:8581–8590
30. Merkler D, Horvath E, Bruck W, Zinkernagel RM, Del la Torre JC, Pinschewer DD (2006) "Viral deja vu" elicits organ-specific immune disease independent of reactivity to self. J Clin Invest 116:1254–1263
31. Oldstone MB, von Herrath M, Evans CF, Horwitz MS (1996) Virus-induced autoimmune disease: transgenic approach to mimic insulin-dependent diabetes mellitus and multiple sclerosis. Curr Top Microbiol Immunol 206:67–83
32. Westall FC (2006) Molecular mimicry revisited: gut bacteria and multiple sclerosis. J Clin Microbiol 44:2099–2104
33. Mohindru M, Kang B, Kim BS (2006) Initial capsid-specific CD4(+) T cell responses protect against Theiler's murine encephalomyelitis-virus-induced demyelinating disease. Eur J Immunol 36:2106–2115
34. McCoy L, Tsunoda I, Fujinami RS (2006) Multiple sclerosis and virus induced immune responses: autoimmunity can be primed by molecular mimicry and augmented by bystander activation. Autoimmunity 39:9–19
35. Jun S, Gilmore W, Callis G, Rynda A, Haddad A, Pascual DW (2005) A live diarrheal vaccine imprints a Th2 cell bias and acts as an anti-inflammatory vaccine. J Immunol 175:6733–6740
36. Sewell DL, Reinke EK, Co DO et al (2003) Infection with Mycobacterium bovis BCG diverts traffic of myelin oligodendroglial glycoprotein autoantigen-specific T cells away from the central nervous system and ameliorates experimental autoimmune encephalomyelitis. Clin Diagn Lab Immunol 10:564–572
37. Green J, Casabonne D, Newton R (2004) Coxsackie B virus serology and type 1 diabetes mellitus: a systematic review of published case-control studies. Diabet Med 21:507–514
38. Filippi C, von Herrath M (2005) How viral infections affect the autoimmune process leading to type 1 diabetes. Cell Immunol 233:125–132
39. Jun HS, Yoon JW (2004) Viral Infections and type1 diabetes. In: Shoenfeld Y, Rose NR (eds) Infection and autoimmunity. 1st edn. Elsevier, Amsterdam, pp 229–249
40. Altobelli E, Petrocelli R, Verrotti A, Valenti M (2003) Infections and risk of type I diabetes in childhood: a population-based case-control study. Eur J Epidemiol 18:425–430
41. King C, Ilic A, Koelsch K, Sarvetnick N (2004) Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell 117:265–277
42. Gronski MA, Boulter JM, Moskophidis D et al (2004) TCR affinity and negative regulation limit autoimmunity. Nat Med 10:1234–1239
43. Serreze DV, Wasserfall C, Ottendorfer EW et al (2005) Diabetes acceleration or prevention by a coxsackievirus B4 infection: critical requirements for both interleukin-4 and gamma interferon. J Virol 79:1045–1052
44. Alyanakian MA, Grela F, Aumeunier A et al (2006) Transforming growth factor-beta and natural killer T-cells are involved in the protective effect of a bacterial extract on type 1 diabetes. Diabetes 55:179–185
45. Raine T, Zaccone P, Mastroeni P, Cooke A (2006) Salmonella typhimurium infection in nonobese diabetic mice generates immunomodulatory dendritic cells able to prevent type 1 diabetes. J Immunol 177:2224–2233
46. Saunders KA, Raine T, Cooke A, Lawrence CE (2006) Inhibition of autoimmune type 1 diabetes by gastrointestinal helminth infection. Infect Immun 75:397–407
47. Harley JB, James JA (2006) Epstein–Barr virus infection induces lupus autoimmunity. Bull Hosp Joint Dis 64:45–50
48. Harley JB, Harley IT, Guthridge JM, James JA (2006) The curiously suspicious: a role for Epstein–Barr virus in lupus. Lupus 15:768–777
49. James JA, Neas BR, Moser KL et al (2001) Systemic lupus erythematosus in adults is associated with previous Epstein–Barr virus exposure. Arthritis Rheum 44:1122–1136
50. Parks CG, Cooper GS, Hudson LL et al (2005) Association of Epstein–Barr virus with systemic lupus erythematosus: effect modification by race, age, and cytotoxic T lymphocyte-associated antigen 4 genotype. Arthritis Rheum 52:1148–1159
51. Chen CJ, Lin KH, Lin SC et al (2005) High prevalence of immunoglobulin A antibody against Epstein–Barr virus capsid antigen in adult patients with lupus with disease flare: case control studies. J Rheumatol 32:44–47
52. Mockridge CI, Rahman A, Buchan S et al (2004) Common patterns of B cell perturbation and expanded V4–34 immunoglobulin gene usage in autoimmunity and infection. Autoimmunity 37:9–15
53. Bengtsson A, Widell A, Elmstahl S, Sturfelt G (2000) No serological indications that systemic lupus erythematosus is linked with exposure to human parvovirus B19. Ann Rheum Dis 59:64–66
54. Hemauer A, Beckenlehner K, Wolf H, Lang B, Modrow S (1999) Acute parvovirus B19 infection in connection with a flare of systemic lupus erythematodes in a female patient. J Clin Virol 14:73–77
55. Seishima M, Oyama Z, Yamamura M (2003) Two-year follow-up study after human parvovirus B19 infection. Dermatology 206:192–196
56. Hrycek A, Kusmierz D, Mazurek U, Wilczok T (2005) Human cytomegalovirus in patients with systemic lupus erythematosus. Autoimmunity 38:487–491
57. Wang H, Nicholas MW, Conway KL et al (2006) EBV latent membrane protein 2A induces autoreactive B cell activation and TLR hypersensitivity. J Immunol 177:27932–802
58. Chang M, Pan MR, Chen DY, Lan JL (2006) Human cytomegalovirus pp65 lower matrix protein: a humoral immunogen for systemic lupus erythematosus patients and autoantibody accelerator for NZB/W F1 mice. Clin Exp Immunol 143:167–179
59. Mittleman BB, Morse HC 3rd, Payne SM, Shearer GM, Mozes E (1996) Amelioration of experimental systemic lupus erythematosus (SLE) by retrovirus infection. J Clin Immunol 16:230–236
60. Kuroda Y, Nacionales DC, Akaogi J, Reeves WH, Satoh M (2004) Autoimmunity induced by adjuvant hydrocarbon oil components of vaccine. Biomed Pharmacother 58:325–337
61. Satoh M, Hamilton KJ, Ajmani AK et al (1996) Autoantibodies to ribosomal P antigens with immune complex glomerulonephritis in SJL mice treated with pristane. J Immunol 157:3200–3206
62. Saikku P, Leinonen M, Mattila K et al (1988) Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 2:983–986
63. Danesh J, Whincup P, Walker M (2003) Chlamydia pneumoniae IgA titres and coronary heart disease: prospective study and meta-analysis. Eur Heart J 24:881
64. Degre M (2002) Has cytomegalovirus infection any role in the development of atherosclerosis? Clin Microbiol Infect 8:191–195
65. Beck JD, Eke P, Lin D et al (2005) Associations between IgG antibody to oral organisms and carotid intima-medial thickness in community-dwelling adults. Atherosclerosis 183:342–348
66. Frostegård J (2004) Infection and atherosclerosis. In: Shoenfeld Y, Rose NR (eds) Infections and autoimmunity. Elsevier, Amsterdam, pp 701–709
67. Lunardi C, Bason C, Corrocher R, Puccetti A (2005) Induction of endothelial cell damage by hCMV molecular mimicry. Trends Immunol 26:19–24
68. Vliegen I, Herngreen SB, Grauls GE, Bruggeman CA, Stassen FR (2005) Mouse cytomegalovirus antigenic immune stimula-

tion is sufficient to aggravate atherosclerosis in hypercholesterolemic mice. Atherosclerosis 181:39–44
69. Lalla E, Lamster IB, Hofmann MA et al (2003) Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 23:1405–1411
70. Caligiuri G, Rottenberg M, Nicoletti A, Wigzell H, Hansson GK (2001) Chlamydia pneumoniae infection does not induce or modify atherosclerosis in mice. Circulation 103:2834283–2834288
71. Binder CJ, Horkko S, Dewan A et al (2003) Pneumococcal vaccination decreases atherosclerotic lesion formation: molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. Nat Med 9:736–743
72. Cervera R, Asherson RA, Acevedo ML et al (2004) Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 63:1312–1317
73. Uthman I, Tabbarah Z, Gharavi AE (1999) Hughes syndrome associated with cytomegalovirus infection. Lupus 8:775–777
74. van Hal S, Senanayake S, Hardiman R (2005) Splenic infarction due to transient antiphospholipid antibodies induced by acute Epstein–Barr virus infection. J Clin Virol 32:245–247
75. Faghiri Z, Wilson WA, Taheri F, Barton EN, Morgan OS, Gharavi AE (1999) Antibodies to cardiolipin and beta2-glycoprotein-1 in HTLV-1-associated myelopathy/tropical spastic paraparesis. Lupus 8:210–214
76. Blank M, Asherson RA, Cervera R, Shoenfeld Y (2004) Antiphospholipid syndrome infectious origin. J Clin Immunol 24:12–23
77. Blank M, Krause I, Magrini L et al (2006) Overlapping humoral autoimmunity links rheumatic fever and the antiphospholipid syndrome. Rheumatology (Oxford, England) 45:833–841
78. Cervera R, Gomez-Puerta JA, Espinosa G, Cucho M, Font J (2003) "CAPS registry". A review of 200 cases from the International Registry of patients with the Catastrophic Antiphospholipid Syndrome (CAPS). Ann Rheum Dis 62(Suppl 1):88
79. Bucciarelli S, Espinosa G, Cervera R et al (2006) Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 54:2568–2576
80. Gharavi EE, Chaimovich H, Cucurull E et al (1999) Induction of antiphospholipid antibodies by immunization with synthetic viral and bacterial peptides. Lupus 8:449–455
81. Zampieri S, Ghirardello A, Iaccarino L et al (2006) Polymyositis–dermatomyositis and infections. Autoimmunity 39:191–196
82. Nishikai M (1994) Coxsackievirus infection and the development of polymyositis/dermatomyositis. Rheumatol Int 14:43–46
83. Mamyrova G, Rider LG, Haagenson L, Wong S, Brown KE (2005) Parvovirus B19 and onset of juvenile dermatomyositis. J Am Med Assoc 294:2170–2171
84. Tam PE, Weber-Sanders ML, Messner RP (2003) Multiple viral determinants mediate myopathogenicity in coxsackievirus B1-induced chronic inflammatory myopathy. J Virol 77:11849–11854
85. Morrison TE, Whitmore AC, Shabman RS, Lidbury BA, Mahalingam S, Heise MT (2006) Characterization of Ross River virus tropism and virus-induced inflammation in a mouse model of viral arthritis and myositis. J Virol 80:737–749
86. Andrade SG, Campos RF, Sobral KS, Magalhaes JB, Guedes RS, Guerreiro ML (2006) Reinfections with strains of *Trypanosoma cruzi*, of different biodemes as a factor of aggravation of myocarditis and myositis in mice. Rev Soc Bras Med Trop 39: 1–8
87. Ohtsuka T, Yamazaki S (2005) Altered prevalence of human parvovirus B19 component genes in systemic sclerosis skin tissue. Br J Dermatol 152:1078–1080
88. Namboodiri AM, Rocca KM, Kuwana M, Pandey JP (2006) Antibodies to human cytomegalovirus protein UL83 in systemic sclerosis. Clin Exp Rheumatol 24:176–178
89. Kalabay L, Fekete B, Czirjak L et al (2002) *Helicobacter pylori* infection in connective tissue disorders is associated with high levels of antibodies to mycobacterial hsp65 but not to human hsp60. Helicobacter 7:250–256
90. Lunardi C, Bason C, Navone R et al (2000) Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells. Nat Med 6:1183–1186
91. Gavanescu I, Pihan G, Halilovic E, Szomolanyi-Tsuda E, Welsh RM, Doxsey S (2004) Mycoplasma infection induces a scleroderma-like centrosome autoantibody response in mice. Clin Exp Immunol 137:288–297
92. Rodriguez-Pla A, Stone JH (2006) Vasculitis and systemic infections. Curr Opin Rheumatol 18:39–47
93. Eden A, Mahr A, Servant A et al (2003) Lack of association between B19 or V9 erythrovirus infection and ANCA-positive vasculitides: a case-control study. Rheumatology (Oxford) 42:660–664
94. Helweg-Larsen J, Tarp B, Obel N, Baslund B (2002) No evidence of parvovirus B19, *Chlamydia pneumoniae* or human herpes virus infection in temporal artery biopsies in patients with giant cell arteritis. Rheumatology (Oxford) 41:445–449
95. Chang LY, Chiang BL, Kao CL et al (2006) Lack of association between infection with a novel human coronavirus (HCoV), HCoV-NH, and Kawasaki disease in Taiwan. J Infect Dis 193:283–286
96. Robinson JL, Spady DW, Prasad E, McColl D, Artsob H (2005) Bartonella seropositivity in children with Henoch–Schonlein purpura. BMC Infec Dis 5(1):21
97. Steed AL, Barton ES, Tibbetts SA et al (2006) Gamma interferon blocks gammaherpesvirus reactivation from latency. J Virol 80:192–200
98. Shinohara H, Nagi-Miura N, Ishibashi K et al (2006) Beta-mannosyl linkages negatively regulate anaphylaxis and vasculitis in mice, induced by CAWS, fungal PAMPS composed of mannoprotein-beta-glucan complex secreted by *Candida albicans*. Biol Pharm Bull 29:1854–1861
99. Malipiero U, Koedel U, Pfister HW et al (2006) TGFbeta receptor II gene deletion in leucocytes prevents cerebral vasculitis in bacterial meningitis. Brain 129(Pt 9):2404–2415
100. Huugen D, Xiao H, van Esch A et al (2005) Aggravation of anti-myeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumor necrosis factor-alpha. Am J Pathol 167:47–58
101. Gottenberg JE, Pallier C, Ittah M et al (2006) Failure to confirm coxsackievirus infection in primary Sjogren's syndrome. Arthritis Rheum 54:2026–2028
102. Fleck M, Kern ER, Zhou T, Lang B, Mountz JD (1998) Murine cytomegalovirus induces a Sjogren's syndrome-like disease in C57Bl/6-lpr/lpr mice. Arthritis Rheum 41:2175–2184
103. Watanabe S, Suzuki K, Kawauchi Y et al (2003) Kinetic analysis of the development of pancreatic lesions in mice infected with a murine retrovirus. Clin Immunol 109:212–223
104. Corapcioglu D, Tonyukuk V, Kiyan M et al (2002) Relationship between thyroid autoimmunity and Yersinia enterocolitica antibodies. Thyroid 12:613–617
105. Maki-Ikola O, Heesemann J, Toivanen A, Granfors K (1997) High frequency of Yersinia antibodies in healthy populations in Finland and Germany. Rheumatol Int 16:227–229
106. Hansen PS, Wenzel BE, Brix TH, Hegedus L (2006) Yersinia enterocolitica infection does not confer an increased risk of thyroid antibodies: evidence from a Danish twin study. Clin Exp Immunol 146:32–38

107. Mandac JC, Chaudhry S, Sherman KE, Tomer Y (2006) The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology (Baltimore) 43:661–672
108. Minelli R, Coiro V, Valli MA et al (2005) Graves' disease in interferon-alpha-treated and untreated patients with chronic hepatitis C virus infection. J Investig Med 53:26–30
109. Nagayama Y, Saitoh O, McLachlan SM, Rapoport B, Kano H, Kumazawa Y (2004) TSH receptor-adenovirus-induced Graves' hyperthyroidism is attenuated in both interferon-gamma and interleukin-4 knockout mice; implications for the Th1/Th2 paradigm. Clin Exp Immunol 138:417–422
110. Saitoh O, Nagayama Y (2006) Regulation of Graves' hyperthyroidism with naturally occurring CD4+CD25+ regulatory T cells in a mouse model. Endocrinology 147:2417–2422
111. Harii N, Lewis CJ, Vasko V et al (2005) Thyrocytes express a functional toll-like receptor 3: overexpression can be induced by viral infection and reversed by phenylmethimazole and is associated with Hashimoto's autoimmune thyroiditis. Mol Endocrinol (Baltimore) 19:1231–1250
112. Nagayama Y, Watanabe K, Niwa M, McLachlan SM, Rapoport B (2004) Schistosoma mansoni and alpha-galactosylceramide: prophylactic effect of Th1 Immune suppression in a mouse model of Graves' hyperthyroidism. J Immunol 173:2167–2173
113. Cunha-Neto E, Bilate AM, Hyland KV, Fonseca SG, Kalil J, Engman DM (2006) Induction of cardiac autoimmunity in Chagas heart disease: a case for molecular mimicry. Autoimmunity 39:41–54
114. Fairweather D, Rose NR (2005) Inflammatory heart disease: a role for cytokines. Lupus 14:646–651
115. Kotilainen P, Lehtopolku M, Hakanen AJ (2006) Myopericarditis in a patient with Campylobacter enteritis: a case report and literature review. Scand J Infec Dis 38(6–7):549–552
116. Fairweather D, Frisancho-Kiss S, Yusung SA et al (2005) IL-12 protects against coxsackievirus B3-induced myocarditis by increasing IFN-gamma and macrophage and neutrophil populations in the heart. J Immunol 174:261–269
117. Omura T, Yoshiyama M, Hayashi T et al (2005) Core protein of hepatitis C virus induces cardiomyopathy. Circ Res 96:148–150
118. Richer MJ, Fang D, Shanina I, Horwitz MS (2006) Toll-like receptor 4-induced cytokine production circumvents protection conferred by TGF-beta in coxsackievirus-mediated autoimmune myocarditis. Clin Immunol 121(3):339–349
119. Afanasyeva M, Rose NR (2004) Viral infection and heart disease: autoimmune mechanisms. In: Shoenfeld Y, Rose NR (eds) Infection and autoimmunity. Elsevier, Amsterdam
120. Green C, Elliott L, Beaudoin C, Bernstein CN (2006) A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. Am J Epidemiol 164:615–623 (discussion 24–28)
121. Oliveira AG, Rocha GA, Rocha AM et al (2006) Isolation of *Helicobacter pylori* from the intestinal mucosa of patients with Crohn's disease. Helicobacter 11:2–9
122. Pronai L, Schandl L, Orosz Z, Magyar P, Tulassay Z (2004) Lower prevalence of *Helicobacter pylori* infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease—antibiotic use in the history does not play a significant role. Helicobacter 9:278–283
123. Saebo A, Vik E, Lange OJ, Matuszkiewicz L (2005) Inflammatory bowel disease associated with Yersinia enterocolitica O:3 infection. Eur J Intern Med 16:176–182
124. Romero C, Hamdi A, Valentine JF, Naser SA (2005) Evaluation of surgical tissue from patients with Crohn's disease for the presence of *Mycobacterium avium* subspecies paratuberculosis DNA by in situ hybridization and nested polymerase chain reaction. Inflamm Bowel Dis 11:116–125
125. Polymeros D, Bogdanos DP, Day R, Arioli D, Vergani D, Forbes A (2006) Does cross-reactivity between *Mycobacterium avium* paratuberculosis and human intestinal antigens characterize Crohn's disease? Gastroenterology 131:85–96
126. Weinstock JV (2004) Inflammatory bowel disease. In: Shoenfeld Y, Rose NR (eds) Infection and Autoimmunity. 1st edn. Elsevier, Amsterdam, pp 649–673
127. Gionchetti P, Rizzello F, Lammers KM et al (2006) Antibiotics and probiotics in treatment of inflammatory bowel disease. World J Gastroenterol 12:3306–3313
128. Sydora BC, Tavernini MM, Doyle JS, Fedorak RN (2005) Association with selected bacteria does not cause enterocolitis in IL-10 gene-deficient mice despite a systemic immune response. Dig Dis Sci 50:905–913
129. Moreels TG, Nieuwendijk RJ, De Man JG et al (2004) Concurrent infection with Schistosoma mansoni attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid induced colitis in rats. Gut 53:99–107
130. Hunter MM, Wang A, Hirota CL, McKay DM (2005) Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis. J Immunol 174:7368–7375
131. Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV (2005) *Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology 128:825–832
132. Szyper-Kravitz M, Shoenfeld Y (2005) Thrombocytopenic conditions—autoimmunity and hypercoagulability: commonalities and differences in ITP, TTP, HIT and APS. Am J Hematol 80:232–242
133. Suzuki T, Matsushima M, Masui A et al (2005) Effect of *Helicobacter pylori* eradication in patients with chronic idiopathic thrombocytopenic purpura—a randomized controlled trial. Am J Gastroenterol 100:1265–1270
134. Stasi R, Rossi Z, Stipa E, Amadori S, Newland AC, Provan D (2005) *Helicobacter pylori* eradication in the management of patients with idiopathic thrombocytopenic purpura. Am J Med 118:414–419
135. Musaji A, Meite M, Detalle L et al (2005) Enhancement of autoantibody pathogenicity by viral infections in mouse models of anemia and thrombocytopenia. Autoimmunity Rev 4:247–252
136. Li Z, Nardi MA, Karpatkin S (2005) Role of molecular mimicry to HIV-1 peptides in HIV-1-related immunologic thrombocytopenia. Blood 106:572–576
137. van Sorge NM, van den Berg LH, Jansen MD, van de Winkel JGJ, van der Pol WL (2004) Infection and Guillain-Barré syndrome. In: Shoenfeld Y, Rose NR (eds) Infection and autoimmunity. Elsevier, Amsterdam, pp 591–612
138. Tam CC, Rodrigues LC, Petersen I, Islam A, Hayward A, O'Brien SJ (2006) Incidence of Guillain–Barre syndrome among patients with Campylobacter infection: a general practice research database study. J Infect Dis 194:95–97
139. Kountouras J, Deretzi G, Zavos C et al (2005) Association between *Helicobacter pylori* infection and acute inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol 12:139–143
140. Watanabe K, Kim S, Nishiguchi M, Suzuki H, Watarai M (2005) Brucella melitensis infection associated with Guillain–Barre syndrome through molecular mimicry of host structures. FEMS Iimmunol Med Microbiol 45:121–127
141. Godschalk PC, Heikema AP, Gilbert M et al (2004) The crucial role of *Campylobacter jejuni* genes in anti-ganglioside antibody induction in Guillain–Barre syndrome. J Clin Invest 114:1659–1665
142. Geier MR, Geier DA, Zahalsky AC (2003) Influenza vaccination and Guillain–Barre syndrome. Clin Immunol 107:116–121

143. Fae KC, Oshiro SE, Toubert A, Charron D, Kalil J, Guilherme L (2005) How an autoimmune reaction triggered by molecular mimicry between streptococcal M protein and cardiac tissue proteins leads to heart lesions in rheumatic heart disease. J Autoimmun 24:101–109
144. Fae K, Kalil J, Toubert A, Guilherme L (2004) Heart infiltrating T cell clones from a rheumatic heart disease patient display a common TCR usage and a degenerate antigen recognition pattern. Mol Immunol 40:1129–1135
145. Guilherme L, Fae K, Oshiro SE, Kalil J (2005) Molecular pathogenesis of rheumatic fever and rheumatic heart disease. Expert Rev Mol Med 7:1–15
146. Olive C, Ho MF, Dyer J et al (2006) Immunization with a tetraepitopic lipid core peptide vaccine construct induces broadly protective immune responses against group A streptococcus. J Infect Dis 193:1666–1676
147. Giovannoni G (2006) PANDAS: overview of the hypothesis. Adv Neurol 99:159–165
148. Perlmutter SJ, Leitman SF, Garvey MA et al (1999) Therapeutic plasma exchange and intravenous immunoglobulin for obsessive–compulsive disorder and tic disorders in childhood. Lancet 354:1153–1158
149. Singer HS, Loiselle CR, Lee O, Minzer K, Swedo S, Grus FH (2004) Anti-basal ganglia antibodies in PANDAS. Mov Disord 19:406–415
150. Jablonka E, Lamb M (2005) Evolution in four dimensions, 1st edn. MIT Press, Boston
151. Lederberg J (2000) Infectious history. Science 288:287–293