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PART 2: CHAPTERS 8 - 14

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8.1 Infections: Cause of autoimmunity, and immune programming

Almost all autoimmune disorders have had an infectious agent raised as a possible aetiological agent. The possible mechanisms for this, and supporting animal evidence, are discussed above. The topic is extensively reviewed in Shoenfeld and Rose 2004. Infections are also important as a secondary feature of autoimmune diseases themselves – thus type 1 diabetes leads to marked increased susceptibility to infection.

There are autoimmune diseases in which infection clearly plays the key role and others where the evidence is less certain. Three examples are given below. ***Table 4.x*** illustrates the range of autoimmune diseases with a putative infectious aetiology.

8.1.1 Rheumatic fever

Rheumatic fever classically follows pharyngeal infection with a few specific M serotypes of group A streptococcus. Whilst the diagnosis of rheumatic fever may be problematic, since there is no single pathognomic feature, the use of standardized criteria such as the Jones criteria has permitted extensive epidemiological description. The disease has been in decline for over a hundred years, with an acceleration since the availability of antibiotics. However it continues to be a feature of communities who suffer from poverty and specifically some of Polynesian ancestry. The disease is clearly associated temporally with the pharyngeal infection and epidemics are seen from time to time. Yet the organism has rarely been isolated from the affected tissues. A number of strands of evidence suggest that the mechanism is in fact autoimmune:

1. Patients with rheumatic fever have heart reactive antibodies in their sera. In addition these antibodies are at higher titre than in people with streptococcal infection and no rheumatic fever. In addition they persist for up to 3 years following an acute attack – the period of time at which patients are at risk of recrurrence. A rise in antibodies is seen at the time of second attacks when these are associated with carditis.
2. Patients also have antibodies to myosin which cross-react with the M protein of the streptococcus.
3. In those patients who develop chorea, the typical neurological complication of rheumatic fever, antibodies against the caudate nucleus of the central nervous system are present. These antibodies correlate with clinical disease activity.

In addition to these antibody patterns both lymphocytes and macrophages aggregate at the site of tissue damage in the heart.

The weight of this evidence strongly suggests that rheumatic fever, and subsequent rheumatic heart disease, is an autoimmune disorder triggered by cross reactive proteins in particular strains of group A streptococci.

Autoimmune Disease	**Possible infectious causes**
Anti-phospholipid syndrome	Pneumonia, urinary tract infection, HCV, HIV
Bechcet's syndrome	HSV, Streptococci
Chagas disease	Trypanosoma cruzi
Diabetes type 1	Coxsackie virus, enteroviruses, CMV
Gastric autoimmunity	Helicobacter pylori
Guillain Barre syndrome	Campylobacter jejuni, Haemophilus influenzae, CMV
Idiopathic thrombocytopenic purpura	HSV, HCV, VZV, EBV, CMV, Helicobacter pylori,
Inflammatory Bowel Disease	Clostidium difficile, Mycobacterium paratuberculosis, measles
Liver disease (Primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis)	HCV, HDV, HSV, enteric bacteria
Multiple sclerosis	A huge range of agents
Paediatric Autoimmune Neuropsychiatric Disorders (PANDAS)	Streptococci
Pemphigus	HSV, HHV8, EBV, HIV, CMV
Polymyositis/dermatomyositis	Coxsackie virus, parvovirus, enterovirus, HTLV, HIV, Toxoplasma, Borrelia
Reiter's syndrome	Shigella, chlamydia
Rheumatic fever	Streptococcus
Systemic sclerosis	Parvovirus B19, CMV, EBV, endogenous retrovirus, Helicobacter pylori
Thyroid disease	Yersinia enterocolitica, enteroviruses, retroviruses
Vasculitis	HBV, HCV, Staphyloccocus aureus

8.1.2 Hepatitis C virus.

This virus, which is predominantly transmitted by contaminated needles and blood products, leads to persistent infection in >80% of those infected. Those persistently infected have been found to have a high prevalence of autoantibodies; Anti-nuclear antibody and rheumatoid factor being those most commonly detected. The exact prevalence of these varies from series to series – for example ANA has been reported in the range of 4 to 41% of patients. This variation is most probably dependent on the variability in methods used for their detection. Nevertheless it is well above the range seen in healthy individuals (2-3%). One intriguing aspect of this association is that it appears to vary geographically – a recent study found a gradient of prevalence in ANA antibodies amongst HCV patients with higher prevalence in the south of Europe versus the north (Yee et al 2004).

Autoimmune disease may be associated with these antibodies. Vasculitis is a well recognized complication of persistent hepatitis C infection and is associated with cryoglobulinaemia. The presence of anti-cardiolipin antibodies in association with clinical thrombosis has been reported in these patients. The true incidence of these events has not been determined. Glomerulonephritis is a well described association with HCV. These patients frequently have hypocomlementaemia and circulating cryoglobulins. More controversial is a putative association with Sjogren's syndrome with some authors claiming that 10-20% of patients may be affected and others refuting this. Anti-Ro and anti-La antibodies do not appear to be markedly increased in HCV infected subjects but there is a suggestion that sialoadenitis, occasionally with sicca symptoms does occur at increased frequency. Similarly discrepant reports apply to the occurrence of thyroid disease. Although it is clear that autoimmune thyroid disease is associated with the interferon alpha therapy that many of these patients receive.

In summary autoantibodies are clearly increased in subjects with persistent HCV infection. The true incidence of autoimmune diseases in comparison to an appropriate control group is yet to be determined although there is good evidence to suggest that some associations do exist.

8.1.3 Multiple sclerosis

Multiple sclerosis is perhaps the autoimmune disorder par excellence that has been purported to result from an infection. It has a striking age incidence curve beginning in the late teens, rising to a peak in the early thirties and then falling to virtually zero by middle life. It has been proposed that this represents a shift of the age incidence curve of childhood infections into adult life i.e.

that the disease is a result of a common childhood infection in a susceptible individual with long latency. The list of agents that have been proposed at one time or another is long including human herpes virus type 6, measles, rabies, paramyxovirus, coronavirus, varicella zoster virus, rubella, mumps and retroviruses (Murray 2002). Even bacteria have been proposed – including Chlamydia pneumoniae and Borrelia burgdorferi. However the current favourite is Epstein Barr virus. Martyn et al (1993) showed that there was a markedly elevated risk of multiple sclerosis amongst patients who both were positive for EBV infection and reported acute glandular fever in adolescence. A subsequent study using the Harvard nurses cohort (Ascherio et al 2001) demonstrated elevated EBV antibodies in those who went on to develop multiple sclerosis versus those who did not. This evidence is epidemiologically persuasive. However it is likely that both genetic and other environmental (see section on UV radiation below) factors play important roles in the aetiology. A large scale, ongoing, incident case control study looking at multiple factors and their interplay in Australia promises some answers.

8.1.4 Immune programming

Most hypotheses relating infection to autoimmunity have assumed that infection has a direct causal role. However an alternative is that infection prepares the ground for the seed that is the actual cause of disease. Infections are known to be critical to current immune responsiveness – HIV is an obvious example, but measles, Epstein-Barr virus and many others are known to modify the immune response both in the short term and over longer periods. Infections also appear to influence the immune system qualitatively – the strong epidemiological evidence for a shift in T_H1/T_H2 balance related to early life infection is now receiving direct biological support from the measurement of cytokines (von Hertzen 2000) Although the exact mechanisms and influences that programme the immune system need to be clarified (Hall et al 2002), as do relationships between programming and cumulative risks. One method for examining the role of early life programming on autoimmunity is co-morbidity. Here there is controversy – some authors (Tremlett et al 2002) claiming an inverse relationship between allergic and autoimmune disorders at the individual level, whilst others find no relationship (Sheikh et al 2003)

In summary it is highly likely that infection plays a role in many autoimmune disorders although the agent and mechanism may differ from one to another. Chemical agents may play an important role in interacting with infections – an area that has hardly been studied. Whether this is so or not infection must be controlled in any epidemiological study since it is a potential confounder of relationships to chemicals.

8.2 Vaccine-related factors

Readers interested in vaccination should also see the section on mercury with respect to thiomersal which is used as a preservative in some killed vaccines.

8.2.1 Vaccines themselves

Whilst there is considerable theoretical basis for vaccination triggering autoimmune phenomena – in many of the same ways as natural infection – the main interest in this has arisen from public concern (Offit & Hackett, 2003). Concern has been particularly focussed on two diseases – multiple sclerosis and type 1 diabetes.

The concern with multiple sclerosis arose with hepatitis B vaccination in France. The original concern came from a case series in a specialist neurological centre. Subsequently case control studies and cohort studies, particularly utilising computerised prescription databases, failed to demonstrate any association. The evidence was reviewed at a meeting at WHO and the conclusion reached that there was no association (Hall et al 1999).

The association between vaccination and type 1 diabetes arose from the observation that type 1 diabetes is rising and this is associated with increasing uptake of vaccination by the population. Some small studies suggested a link. However a recent major Danish record linkage study conclusively showed no relationship between the two (Hviid et al 2004).

Arthritis has been described following administration of hepatitis B, rubella, mumps and measles, influenza, DPT and typhoid vaccine. These are rare occurrences and causality is difficult to establish. However it does appear that rubella vaccination may in genetically susceptible individuals lead rarely to an arthropathy.

Guillain Barre syndrome was particularly associated with “swine flu” vaccine in 1976. It has rarely been associated with other vaccines – tetanus toxoid, BCG, rabies, smallpox, mumps, rubella, hepatitis B, diphtheria, polio.

8.2.2 Vaccine additives

Mercury is clearly immune modulatory in sufficient dose. Since it is a constituent part of Thimerosal, used as a preservative in killed vaccines, concern has been raised concerning its role in immune mediated diseases and autism. The same Danish group, in a separate register based

study (Madsen et al 2003), were able to show no relationship between thimerosal and autism – the primary disease of concern to the public. Again there does not appear to be any scientific evidence to support the public concern.

Alum is used as an adjuvant in several vaccines. It is a poor inducer of cell mediated immunity and there is no evidence of it leading to autoimmunity.

8.3 Dietary Factors

There is considerable interest in research on the influence of dietary factors on autoimmune diseases. This is a broad area that includes caloric intake, specific nutrients and foods, and dietary supplements. Coeliac disease is an example of an autoimmune disease with a clear dietary link – the immunologic response to specific proteins in wheat, barley, and rye producing autoantibodies directed against tissue transglutaminase and mucosal damage in the small intestine. The role of iodine in autoimmune thyroid diseases is discussed in **Chapter __.** The following summary of dietary factors focuses on experimental studies using animal models and human studies of the etiology and progression of multiple sclerosis, type 1 diabetes, inflammatory bowel diseases, rheumatoid arthritis and lupus. The basis for much of this research is the general immunomodulating effect of dietary components, particularly with respect to cytokine production and inflammation. Other effects are more relevant to specific diseases (e.g., demyelination, platelet aggregation). In general, data from studies in humans are more limited and less consistent than the animal literature.

8.3.1 Caloric restriction and leptin

The hormone leptin is produced by adipocytes and is involved in the regulation of food intake and obesity. Periods of caloric restriction inhibit production of leptin. Fasting can improve symptoms in some patients with rheumatoid arthritis (possibly through an anti-inflammatory effect of fasting mediated through leptin), but the effects are not sustained when the fasting period is over (Muller et al., 2001). In mouse models of multiple sclerosis (experimental autoimmune encephalomyelitis) and type 1 diabetes, leptin secretion was closely linked to disease onset (Sanna et al., 2003; Materese et al., 2002). Recent studies report an effect of leptin on T cell stimulation and production of pro-inflammatory cytokines (Sanchez-Margalet et al., 2003). Caloric restriction in lupus mouse models inhibits the disease process and prolongs survival (Leiba et al., 2001).

8.3.2 Dietary fat and fatty acid content

The type and amount of fat in foods is an important aspect of nutrition, with implications for atherosclerosis, cardiovascular disease, and obesity as well as for immune-mediated diseases. The fatty acid composition of foods is determined by the length of the carbon chain and the number and location of double bonds. The "n-3" or "omega-3" fatty acids are those with one or more double bonds, the first of which is located at the third carbon from the omega end of the carbon chain. The essential fatty acids are those that can not be synthesized, and so are only available from foods or supplements. Animal fats are a source of arachidonic acid (an omega-6 fatty acid) and fish is a source of the omega-3 fatty acids ecoisapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA can also be converted from alpha-linoleic acid, found in green leafy vegetables, flaxseed, and canola oils. Arachidonic acid and EPA are the specific fatty acid precursors for the synthesis of specific prostaglandins (PGE) and leukotrines (LTE). The relative balance of different prostaglandins and leukotrines affects the inflammatory response. Arachidonic acid is converted to PGE_2 and LTE_4, which are pro-inflammatory, stimulating natural killer cell activity and pro-inflammatory cytokines (e.g., interleukin-1 and tumor necrosis factor–alpha). EPA is converted to the more anti-inflammatory compounds PGE_3 and LTE_5 (Calder, 1997; Simopoulos, 2002).

Because of the potential effects on inflammation and immune-mediated function, there has been considerable interest in the potential therapetic role of omega-3 fatty acids in autoimmune disease. Most studies in humans have been among patients with rheumatoid arthritis. The randomized clinical trials tend to be relatively small, but there is some evidence of improvement in terms of reduced joint count and morning stiffness in trials of fish oil supplementation (Fortin et al., 1995). There have also been some small trials ($n < 30$) of omega-3 supplementation in patients with systemic lupus erythematosus, but these studies were conducted before the adoption of standardized measures of disease activity and damage. In general, some improvements in lipid profiles and inflammatory measures have been seen, but there are mixed results with respect to improvements in clinic status. (Leiba et al., 2001). In a large observational (non-randomized) study in Japan, there was no association between intake of total fat, type of fat or omega 3 fatty acids and subsequent disease activity among 216 lupus patients (Minami et al., 2003). In ulcerative colitis and Crohn's disease, trials of omega-3 (fish oil) supplements have reported improvements in terms of decreased steroid dosage, decreased disease activity, prolonged periods of remission and increased weight gain, but there are

inconsistencies between observed effects among studies and long-term benefits have been difficult to demonstrate (Belluzzi, 2002).

Relatively few studies have been conducted examining fats and fatty acid intake in relation to risk of developing specific autoimmune diseases. In a recent analysis of risk of multiple sclerosis in two large cohorts of women, no association was seen with total fat, monounsaturated fat, total n-6 or total n-3 polyunsaturated fats (Zhang et al., 2000). There is some suggestion from case-control studies of a protective effect of fish or omega-3 fatty acids on risk of developing rheumatoid arthritis (Pattison et al., 2004) but there are currently no prospective studies analyzing dietary intake of fats in relation to risk of rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel diseases.

8.3.3 Antioxidants

The influence of antioxidants (e.g., vitamin E or alpha-tocopherol, vitamin C or ascorbic acid, and carotenoids including beta-carotene and lycopene) on autoimmune diseases has not been studied extensively. There is some evidence that damage induced by reactive oxygen species contributes to the destruction of pancreatic beta cells, brain tissue, and joints seen in type 1 diabetes, multiple sclerosis and rheumatoid arthritis, respectively. However, there are few prospective studies of antioxidant intake and risk of autoimmune diseases. Although there is some evidence of a reduced risk of rheumatoid arthritis and lupus with higher intake or serum levels of antioxidants, there are inconsistent findings with respect to which antioxidants or foods are involved. (Comstock et al., 1997; Knekt et al., 2001; Cerhan et al., 2003) . Only one prospective study of antioxidants and risk of multiple sclerosis is available, and that study reported no association with intakes of vitamin C, vitamin E, or carotenoids (Zhang et al., 2001).

8.3.4 Vitamin D

Vitamin D can be obtained from some foods, but its major source is through the action of ultraviolet radiation which converts 7-dehydrocholesterol to cholecalciferol in the skin. Hydroxylation of this compound in the liver produces 25-hydroxycholecalciferol [25-OHD_3], which is then converted in the kidney to 1,25-hydroxycholecalciferol [1,25-$(OH)_2D_3$], the active form of vitamin D. Vitamin D plays a major role in promoting absorption of calcium and maintaining bone mineralization. Recently research has focused on immunosuppressive effects of Vitamin D. The vitamin D receptor has been detected in lymphocytes and the thymus, and vitamin D plays a role in T-cell mediated immune response (Deluca & Cantorna, 2001).

Most of the human studies of vitamin D and autoimmune diseases have focused on type 1 diabetes and multiple sclerosis. Higher risks of these diseases are generally seen at higher latitudes (e.g., further north in the northern hemisphere and further south in the southern hemisphere), which would be areas of relatively low exposure to ultraviolet radiation (Ponsonby et al., 2002). Case-control and prospective studies of maternal and child vitamin D intake have provided some evidence of a protective effect of vitamin D on risk of developing type 1 diabetes (Zella & DeLuca, 2003; Fronczak et al., 2003). Prospective studies have also reported a reduced risk of multiple sclerosis (Munger et al., 2004) and rheumatoid arthritis (Merlino et al., 2004) in women with higher intakes of vitamin D. The relative contribution of foods and supplements to the protective effects seen in these studies is not clear.

In murine models of experimental autoimmune encephalomyelitis (multiple sclerosis), type 1 diabetes, and inflammatory bowel disease, treatment with 1,25-$(OH)_2D_3$ (in conjunction with adequate calcium intake) has been shown to inhibit the development of disease (Van Amerongen et al., 2004; Hypponen, 2004; Froicu et al., 2003). In lupus mouse strains, however, a more complex situation is seen, with some evidence of worsening of disease (particularly with respect to measures of renal damage) with 1,25-$(OH)_2D_3$ treatment (Vaisberg et al., 2000).

8.3.5 L-Tryptophan

Eosinophilia Myalgia Synydrome (EMS) is a multi-systemic, autoimmune disease that was first diagnosed in 1989 and was associated with the use of contaminated L-tryptophan (Hertzman et al., 1990). An essential amino acid and seratonin precursor, L-tryptophan is used to treat depression, premenstrual syndrome, and insomnia. In nine months, 1658 people were diagnosed with the disease in the United States, Germany and Belgium (Swygert et al., 1990; Andre et al., 1991; Carr et al., 1994). A product recall dramatically reduced the number of new cases reported, although approximately 3% of EMS patients did not use L-trptophan (Swygert et al., 1990). Rare non-L-tryptophan-associated cases continue to be reported (Margolin, 2003). Although EMS was most frequently reported in women (84%), non-Hispanic whites (97%), and residents of western states (Swygert et al., 1990), statistical analysis showed no correlation with duration of L-tryptophan intake, concurrent medications (Kamb et al., 1992; Carr et al., 1994; Kaufman & Krupp, 1995), gender or race, since the majority of people using these products are female (60%) and white (80%). There have been associations with dose, age of the patient (average 48 years), and a single supplier that had made changes in the manufacturing process

preceding the epidemic (Swygert et al., 1990; Kamb et al., 1992; Das et al., 2004). The hallmark manifestations of EMS are profound eosinophilia (>1000 cells/mm3) and debilitating myalgia (Swygert et al., 1990); other symptoms include: serum antinuclear antibodies targeting lamin C and three unique disease specific proteins (Kaufman et al., 1991; Varga et al., 1992; Kaufman et al., 1995a), fasciitis, arthralgia, peripheral neuropathy, paresthesias, edema, schleroderma, pruritic rash, dyspnea, myopathy, fatigue, muscle cramps, cognitive impairment, increased aldolase levels, and increased liver enzyme levels (Swygert et al., 1990; Hertzman et al., 1995; Kaufman & Krupp, 1995).

Gene expression and protein synthesis of fascial TGF-1β, fibronectin, and Type IV collagen (Peltonen et al., 1991), and fibroblast Type I collagen (Varga et al., 1993; Hitraya et al., 1997) from human EMS affected tissue and cells were increased, compared to controls. These reports suggest that the cytokine TGF-1β, upregulation of collagen genes, and subsequent accumulation of collagen, may play a role in the development of connective tissue alterations, especially diffuse fasciitis and cutaneous fibrosis (Peltonen et al., 1991; Varga et al., 1993). Muscle and fascia from EMS patients revealed an inflammatory exudate composed primarily of activated T cells and macrophages at perimysial, endomysial, perivascular, and fascial sites. CD8+ cells were the dominant T-cell subpopulation and MHC class I antigen complex expression was increased on inflammatory and endothelial cells and muscle fibers, indicating a cell mediated immune response targeting connective tissue. Emslie-Smith, et al. (1991) proposed that a contaminant of L-tryptophan haptenates a connective tissue component, forming a stable, immunogenic complex and initiating an autoimmune response that is augmented by the local release of inflammatory cytokines from activated cells, however the specific cellular target is not yet known.

A higher incidence of mutation in the cytochrome P450 CYP2D6 gene, resulting in the poor metabolizer genotype, and the absence of activity in the corresponding enzyme among EMS cases (n=27) indicate that altered xenobiotic metbolism may play a role in the pathogenesis of EMS (Flockhart et al., 1994). Animal models also suggest a genetic component to EMS susceptibility; autoimmune-prone NZBWF1 mice and Lewis rats have a lower hepatic nuclei binding affinity for case-associated L-tryptophan compared to Swiss mice and Sprague-Dawley rats, respectively (Sidransky and Verney, 1994; Sidransky and Verney, 1997). Two contaminants identified in the tryptophan preparations associated with EMS, 1,1'-Ethylidenebis[L-tryptophan] (EBT) and 3-(phenylamino)-L-alanine (PAA), have been the focus

of further investigation into the etiologic agent (Mayeno et al., 1992; Hill et al., 1993; Simat et al., 1999; Barth et al., 2001). EBT stimulated gene expression and synthesis of Type I collagen in cultured human fibroblasts in a dose dependent manner, suggesting that EBT may be involved in the fibrosis of EMS (Takagi et al., 1995; Zangrilli et al., 1995). In C57BL/6 mice, EBT induced inflammation; fibrosis; increased mast cell proliferation and degranulation; enhanced gene expression for types I, III, and IV collagen, and TGF-1β; and altered metabolism of L-tryptophan by the kynurenine pathway in dermal and subcutaneous tissue (Silver et al., 1994; Suzuki et al., 1996). PAA is chemically similar to 3-(phenylamino)-1,2-propanediol (PAP), one of the candidate etiologic agents for toxic oil syndrome. *In vitro* conversion of PAA to PAP and of PAP to PAA has been demonstrated, (Mayeno et al., 1995; Schurz et al., 1997), suggesting a possible mechanistic connection between TOS and EMS. The true etiologic agent(s) of EMS and the mechanism(s) of action remain elusive, however, the prevailing theories support a combination of genetic susceptibility, haptenation self proteins by L-tryptophan contaminants and subsequent activation of auto-reactive T-cells, and a cell mediated immune response targeting connective tissue.

9. ANIMAL MODELS TO ASSESS CHEMICAL INDUCED AUTOIMMUNITY

9.1 Introduction

The number of animal models of autoimmunity is extensive. These models represent a variety of systemic and organ-specific diseases, and are mostly used to explore etiology and therapeutic possibilities for certain autoimmune diseases.

Etiology in the various models can be based either on spontaneous, genetically predisposed development or on induction with specific antigens (mostly in combination with an adjuvant) infectious agents or chemicals (Chernajovsky et al., 2000; Skaguchi, 2000). Irrespectively of how the disease is induced most models rely on inbred animals, indicating the importance of genetic background and in accordance with the idiosyncratic nature of many autoimmune diseases.

In the case of spontaneous autoimmune diseases mice are most frequently used, and with the advent of transgenic and KO mice the number of genetically predisposed, autoimmune models has increased enormously. For SLE, around 30 different KO models have been described, mostly on MRL background (Chan et al., 1999) and also for diabetes, multiple sclerosis and arthritis new models have been designed using transgenics or KO-technique (Wong et al., 1999; Holmdahl et al., 1999; Goverman, 1999; Chernajovsky et al., 2000). Also modification of the MHC-II genome are being used to design models of autoimmunity (Taneja & David, 1999; Boyton & Altmann, 2002; Das et al., 2000), incidently also in rat (Taurog et al., 1999). Mostly, these new models are used to further study etiology of disease.

On the contrary, chemical-induced autoimmune models are actually rare (Table 13), but based on the multifactorial and idiosyncratic nature of autoimmune diseases it might not be so strange that only few compounds induce clinically apparent autoimmune or autoimmune-like allergic phenomena in animals.

Table 13: Non-comprehensive overview of chemicals that have been shown to induce autoimmune phenomena in animals

Chemically induced		
Rat		
Brown Norway rat	HgCl2	IC-glomerulonephritis
	AU-salts	Skin pathology; dermatitis
	D-Penicillamine	Polyclonal IgE
	Nevirapine	AutoAb (Type IV-collagen, ANA, anti-ACh, anti-thyroglobulin)
	HCB*	Systemic inflammatory response with autoimmune symptoms
Lewis	CyA	Alopecia Graft vs. Host
Mouse		
Various strains with differences in sensitivity (see text)	Procainamide D-Penicillamine HgCl2 Gold salts Hydralazine	ANA, AnolA Splenomegaly anti-fibrillarin anti-insulin
C57BL/Ks	STZ	Type 1 Diabetes
DBA/1 susceptible DBA/2 resistant	Pristane	Pristane induced arthritis
Neonatal mouse	CsA	Multi-organ type inflammation
Cat	6-propylthiouracil	SLE: ANA, Sm antigen lymphadenopathy, hemolytic anemia
Dog		
Beagle Dobberman	Procainamide Sulfonamides Radiocontrast media Etoposide	ANA Multiples symptons including skin eruptions (urticaria) and blood dyscrasias
Chickens		
OS	Iodine	Autoimmune thyroiditis
Monkey		
	L-canavanine (alfa-alfa seeds)	SLE, ANA

see text for more information and references

9.2 Rat models

9.2.1 The Brown Norway rat model

The Brown Norway (BN) rat model is an interesting model (Balazs, 1987; Donker et al., 1984) as a number of chemicals have been shown to induce clinically manifested autoimmune disease in this particular strain of rats. HgCl2 is probably the most scrutinized compound in the BN rat but also D-penicillamine (Tournade et al., 1990), gold-salts (Tournade et al., 1991;

Qasim et al., 1997), hexachlorobenzene (HCB) (Michielsen et al., 1999; Ezendam et al., 2004a; Ezendam et al., 2004b; Vos et al., 1979a) and recently nevirapine (Shenton et al., 2003) have been shown to induce clinical effects. Captopril (Donker et al., 1984) and also felbamate (Popovic et al., 2004) were tested in BN rats as well but, appeared to be ineffective.

Effects that are reported are only partly compound-specific and include both organ-specific effects (glomerulonephritis, splenomegaly, skin rashes) and systemic effects (hyperimmunoglobulinemia, in particular IgE, and increased levels of autoantibodies). Derangements in BN are accompanied by polyclonal lymphoproliferation (both T and B cells) (Hirsch et al., 1986; Hirsch et al., 1982).

BN rats are known as so-called Th2-prone animals (e.g. they are activated to produced high levels of IgE and to display many characteristics of type 2 immune response). This property and/or the underlying genetic trait may be responsible for the high susceptibility of this strain to chemical-induced autoimmune effects and is often brought forward as a drawback of using this strain. But again, as for disease-prone mouse strains, it can also be argued that the inherent susceptibility of this rat strain resembles the inherent susceptibility in human cases of chemical-induced autoimmune disorders.

9.2.1.1 Metals

Autoimmune phenomena in BN rats induced by HgCl2 peak around day 10 after the last of 5 subcutaneous injections. Again 20 days later immune alterations are mostly at control level, and the kidney effects (for instance observed as proteinuria) are clearly less than on day 10 (Aten et al., 1988). In addition, low dose pretreatment of BN rats with HgCl2 prevents development of adverse immunity (Szeto et al., 1999), and neonatal injection of HgCl2 in BN rats renders them tolerant to mercury-induced (but not gold-induced) autoimmune phenomena Field et al., 2000). Remarkably, this tolerance is HgCl2-specific since rats are still susceptible to gold-induced

autoimmunity. These phenomena, transience of autoimmune effects as well as low-dose protection, is shown to be due at least in part to the development of regulatory immune cells. In case of HgCl2, these cells have been identified as either IFN-g-producing CD8+CD45RChigh regulatory T cells (Pelletier et al., 1990; Szeto et al., 1997; Mathieson et al., 1991; Field et al., 2003) or RT6.2+ T cells (Kosuda et al., 1994). In view of this, it is relevant to note that Lewis rats which produce predominantly CD8+ regulatory T cells ('suppressor' T cells)in response to HgCl2, are resistant to HgCl2-induced autoimmunity, and rather display a polyclonal immunosuppressive response(Pelletier et al., 1987). Concordingly with this strain sensitivity, it has been clearly demonstrated that susceptibility to HgCl2 induced autoimmune effects are dependent on MHC-II haplotyp (Aten et al., 1991).

Gold salts also induce a autoimmune syndrome in the BN rat similar to that observed with HgCl2 (and D-penicillamine), with increased IgE levels and vasculitis (observed in the gut) (Balazs, 1987; Qasim et al., 1997).

9.2.1.2. D-Penicillamine

D-Penicillamine induces a autoimmune disease in BN rats that is similar to adverse immune responses seen on some patients (Tournade et al., 1990). Recently, a series of studies have further explored D-penicillamine induced autoimmunity in the BN rat, in particular with respect to immunoregulation (Masson & Uetrecht, 2004). Interestingly, only 60-80% of all treated BN rats develop the autoimmune disease and in addition low dose pretreatment with the D-penicillamine has been shown to tolerize the animals to subsequent normally autoimmunogenic doses (Donker et al., 1984; Masson & Uetrecht, 2004). It appeared that the observed tolerance is mediated by immune cells, including T and non-T cells. This again illustrates that idiosyncracy also occurs in animals and moreover that these diseases are subject to regulatory mechanisms.

9.2.1.3 Hexachlorobenzene

The environmental pollutant hexachlorobenzene (HCB) has also been studied in BN rats but also in Lewis, Wistar and Sprague Dawley rats (see section 7.9 on HCB). It appeared that all rat strains displayed HCB-induced symptoms reminiscent of an autoimmune disease (splenomegaly, increased serum levels of autoantibodies, inflammatory responses in lungs and skin), being the BN rat the most sensitive (Michielsen et al., 1997). This strain-independence already indicates that HCB-induced pathology is probably less or not idiosyncratic. In addition, a clear role of T cells has not been found, although interference with T cell activation with CsA prevented or

delayed a number of T cell dependent responses, such as levels of IgE and eosinophilia in lungs, skin lesions (Ezendam et al., 2004a). Further analyses (e.g. adoptive transfer studies) did not reveal an initiating role of T cells and it seems now that HCB is probably a general inflammatory instead of an autoimmunogenic chemical (Ezendam et al., 2004b), that activates predominantly macrophages and only secondary to this, by some kind of adjuvant signal, also T cells.

9.2.1.4 Nevirapine

Nevirapine is used to treat HIV-infected patients, and in some individuals this drug causes severe skin rash. Similarly, nevirapine has been found to cause skin rash in 100% of high-exposed (150 mg/kg) female BN rats (Shenton et al., 2003). Female Sprague Dawley rats were less sensitive (21% or rats showed a rash), and male BN or Sprague Dawley rats, and female Lewis rats were resistant. Low dose pretreatment with nevirapine also (similar to D-penicillamine and HgCl2) induced tolerance to subsequent normal high doses and upon transfer of splenocytes from sick to naive animals nevirapine-induced rash occured earlier. In addition, upon rechallenge with nevirapine the rash developed faster in previously exposed but fully recuperated rats. In all nevirapine-induced disease in BN rats is clearly immune-mediated (Shenton et al., 2003).

9.2.2 Other rat models

9.2.2.1 Cyclosporin A-induced Autoimmunity (CsA-AI)

Cyclosporin (CsA) is able to induce an autoimmune syndrome in Lewis rats, but only when these rats are subjected to lethal (8.5 Gy X irradiation) and reconstituted with syngeneic or autologous bone marrow (Damoiseaux, 2002). About two weeks after cessation of CsA treatment, which starts on the day of the bone marrow transplantation, the rats start to develop autoimmune disease. Acute symptoms of CsA-induced Autoimmunity (CsA-AI) is similar to GvHD, with erythroderma, dermatitis and alopecia and the chronic phase is characterized by progressive alopecia combined with scleroderma-like skin pathology. CyA-AI is clearly immune dependent and involves autoreactive T cells (specific for MHC class II-paptied named CLIP) and requires both an intact thymus and absence of a regulatory T cells (CD45RClowCD4+ phenotype) (Barendrecht et al., 2002). The effect of CsA on the thymus has been subject of many studies and it turned out that CsA inhibits differentation of CD4+CD8+ thymocytes possibly by interference with activation-induced cell death (Shi et al., 1989). This probably is the cause of the increased release of auto-reactive T cells (Kosugi et al., 1989). In line with this and with the protocol required to induce CsA-AI in rat, neonatal administration of CsA in mice also induces a multiorgan-type autoimmune disease (Sakaguchi & Sakaguchi, 1989).

9.3 Mouse models

A number of studies have been performed to induce systemic immunosensitization and autoimmunity (i.e. autoantibody formation or autoreactive T cells) in mice. And again, occurrence of disease appears to be strain-dependent.

9.3.1 Metals

Subcutaneous administration of HgCl2 (Mirtcheva et al., 1989; Kubicka-Muranyi et al., 1995; Kubicka-Muranyi et al., 1996) or intramuscular treatment with Au(I)-salts (Schuhmann et al., 1990) has been shown to induce anti-nuclear and anti-nucleolar autoantibodies (ANA, AnolA) from around 4 weeks of exposure in particular in high responding A.SW mice (MHC-H2s haplotype). Other H2s mice, such as B10s mice are also susceptible, but congenic H2d mice (e.g. B10D2) or H2k mice (B10.BR) are resistant to HgCl2-induced autoimmune effects, indicating the importance of MHC haplotype (Mirtcheva et al., 1989). The response to HgCl2 in A.SW mice is Th2 mediated, involving IL-4 production and increases in IgE and IgG1 levels (Ochel et al., 1991). Interestingly, both H2s and H2d mice responded to HgCl2 exposure with an increase in the number of activated CD4+CD45Rlow effector T cells (van Vliet et al., 1991), implying that the difference between these strains also involves immunoregulatory processes HgCl2 given orally via the drinking water also induced antinucleolar antibodies (IgG-class) in SJL/N (H2s) mice after 10 weeks (Hultman &Enestrom, 1992).

9.3.2 Drugs

Only few drugs have actually been succesfully identified in mice with respect to their potential to induce autoimmune phenomena.

D-penicillamine has been shown to induce anti-ssDNA and anti-insulin antibodies in C57BL/Ks (H2d) and C3H/He (H2k) but not in BALB/c or C57BL/6 mice after subcutaneous exposure for 4 weeks (Brik et al., 1995). Also after oral treatment (for 7 to 8 months, in the drinking water) D-penicillamine (and in the same study also quinidine) induced an increase in auto-antibodies in A.SW/Sn (H2s) mice (Monestier et al., 1994).

The anti-neoplastic drug streptozotocin (STZ) is capable of inducing immune-dependent diabetes mellitis (IDDM) when administered (intraperitoneally) at low dose on 6 consecutive days. Important to note is that a strong dependency on strain and/or gender has been observed, being male C57BL/Ks (H2d) mice most sensitive (Leiter, 1982; Herold et al., 1996). Unlike most other

drugs, STZ appeared to elicit a typical Th1 dependent type 1 response, including a strong activation of macrophages, IFNγ-producing CD4+ and CD8+, and IgG2a antibodies (Albers et al., 1998; Nierkens et al., 2002).

Procainamide has been found to induce an increase in ANA in A/J mice after 8 months of exposure via the drinking water (Layland et al., 2004). This increase appeared mediated by CD25-CD4+ T cells and regulated by CD25+CD4+ regulatory T cells.

Diphenylhydantoin (via drinking water for 6 months) was tested in genetically predisposed mice (C57BL/6-lpr/lpr strain) but the compound was rather depressed levels of autoantibodies (Bloksma et al., 1994), ***(see also part 4.1?)***. In another study (Okada et al., 2001), a slight shift towards a Th2 response was demonstrated by showing an increase in the KLH-induced production of IL-4 and IgE (IgE was detected by direct ELISA, which makes these data doubtful) in a 4 weeks exposure study. However, in this study spleen proliferation responses were also suppressed, and Robinson et al. (1986) have compared in one study a large number of MHC-defined mouse strains with respect to induction of antinuclear autoantibodies by $HgCl_2$ (*subcutaneously*, detected after 0.5 to 2 months), gold salts (*intramuscularly*, detected after 1 to 5 months) and D-penicillamine (*orally*, detected after 4.5 to 5 months) and reported that A.SW mice were high responders to all three chemicals.

9.3.3 Pristane

Pristane (2,6,10,14-tetramethylpentadecane) is a mineral oil known to induced arthritis, also called pristane-induced arthritis (PIA), in an experimental disease model (Wooley & Whalen, 1991). PIA is MHC-haplotype dependent, DBA/1 mice are susceptible whereas DBA/2 are not, and is accompanies by a broad spectrum of autoantibodies (RF, anti-collagen, antibodies to HSP). PIA is clearly immune dependent since nu/nu mice and irradiated mice do not display PIA, and involves in particular CD4+ T cells (Wooley & Whalen, 1991). PIA appeared to involve polyclonal T cell activation (Wooley et al., 1998), and can be protected for by CD4+ Th2 cells specific for HSP65 (Beech et al., 1997).

PIA is also inducible in rat, with DA rats being susceptible and E3 rats being resistant (Wester et al., 2003), and controlled by multiple genes, identified as Pia loci (Olofsson et al., 2003).

9.4. Genetically predisposed animal models

Chemicals may exacerbate autoimmunity in genetically predisposed animals or in induced animal models (Kammuller et al., 1989a). The rationale behind using autoimmune-prone animal strains for the purpose of studying and prediction of autoimmunogenic potential of chemicals is that, apart from being probably very sensitive for adverse immune effects, exacerbation of disease is considered one of the possibilities by which chemicals may elicit autoimmune phenomena (Pollard et al., 1999). As mentioned also the BN rat is a sensitive rat strain for Th2-dependent phenomena, as is the Lewis rat for CsA-AI.

In induced models, a susceptible animal strain is immunized with a mixture of an adjuvant and an autoantigen isolated from the target organ. Examples are adjuvant arthritis (AA) (Pearson, 1956), and experimental allergic encephalomyelitis (EAE) (Ben-Nun & Cohen, 1982) in the Lewis strain rat. Examples of spontaneous models of autoimmune disease are the BB-rat (Mordes et al., 1987; Prins et al., 1991) and the NOD-mouse (McDevitt et al., 1996) that develop autoimmune pancreatitis and subsequently diabetes, or the (NZBxNZW)F_1 or MRL/lpr mouse (Pollard et al., 1999; Shaheen et al., 1999) that spontaneously develop systemic lupus erythematosus (SLE)-like disease.

Induced models (EAE and AA models for instance) are often used to the study of the pathogenesis of and therapeutic venues for relevant autoimmune diseases. These models have been proposed as means to evaluate the immunomodulatory effects of chemicals on ongoing autoimmune diseases in a second tier of immunotoxicity testing.

9.4.1 SLE-prone strains of mice

As a considerable amount of drugs are linked to lupus-like symptoms (e.g. drug-related lupus) and although drug-induced lupus differs from SLE in certain aspects (Pollard et al., 1999; Shaheen et al., 1999), it has been proposed to use SLE-prone strains of mice as model animals to test for the exacerbating and even initiating potential of drugs. Among the mice strains proposed for this purpose are the spontaneous SLE models (BWF1, NZB x SWRF1, MRL/lpr/lpr/Mp, BXSB/Mp, (NZB x NZW)F1, NZM, NZBWF1, AKR). Experience with any of these strains is scarce, and is restricted mainly to salts of heavy metals such as HgCl2 and this chemical had clear immunostimulatory effects in NZBWF1 mice (Pollard et al., 1999). In a study examining the effect of phenythoin (Bloksma et al., 1994), MRL-mice were exposed to the drug in the drinking water for a period of 6 months, but in this case no indications of adverse immune reactions were found. Future studies should include more autoimmunogenic pharmaceuticals and

negative controls in order to decide whether SLE-prone models are indeed applicable as model to study or predict chemical-induced autoimmunity.

9.5 Other species

9.5.1 Dogs

Dogs is a species frequently used in toxicity studies. However, there are only few reports in open literature on dog studies with respect to chemical- or drug-induced hypersensitivity reactions or autoimmune effects, and studies are also often contradicting. For instance, procainamide has been shown to induce lupus like symptoms (mainly increase of antinuclear antibodies) in one study (Balazs & Robinson, 1999), but not in another study with younger dogs (Dubois & Strain, 1972). Similar discrepancies were observed for hydralazine-induced effects in dogs (Kammuller et al., 1989).

More recent reports show clear sulfonamide-induced idiosyncratic responses in dog. The syndrome induced by sulfonamides in dogs (mostly Dobermans) encompass fever, arthropathy blood dyscrasias (neutropenia, thrombocytopenia or hemolytic anemia) hepatopathy, skin eruptions, uveitis and keratoconjunctiviti sicca (Trepanier, 2004). These symptoms start to occur on average as soon as 12 days after start of exposure. However the incidence in dogs (and cats) is as expected from idiosyncrasy, estimated to be around 0.25% (Noli et al., 1995).

Radiographic contrast media have been shown to induce histamine release in a dogs study indicating that they induce pseudo-allergic responses (Ennis et al., 1995). And the anti-neoplastic agent etoposide appeared to cause cutaneous reactions (pruritis, urticaria and swelling in head region and extremities) in dogs (Beagles) upon intravenous exposure (Ogilvie et al., 1988).

9.5.2 Miscellaneous

Apart from the species mentioned, other species used to study chemical induced autoimmune phenomena or systemic hypersensitivity reactions. Experiments (Aucoin, 1989) with cats showed that propylthiouracil (PTU) induces SLE-like phenomena (autoantibodies against nuclear antigen, Smith (Sm) antigen, red blood cells and cytoplasmic components, lymphoadenopathy, weight loss). However, important PTU-induced symptoms, like agranulocytosus and liver toxicity, observed in man are not observed in cat (Shenton et al., 2004). In addition, the finding that symptoms after rechallenge occur with the same delay in time are not supportive for an immunological nature of the phenomena in cat. The model could

also not be reproduced in more recent years for yet unknown reasons, shedding doubt on the usefulness of the PTU-induced cat-model at this moment (Shenton et al., 2004).

Chemical (incl. diet mediated)-induced autoimmune effects in other species have also been documented, but in most if not all cases, they are limited to isolated cases (for review see Kosuda & Bigazzi, 1996). For instance, Monkeys fed alfalfa-seeds developed antibody-induced anemia, chickens (Cornell C strain) receiving excess of iodine developed antibodies against thyroid hormones and lymphocytic thyroiditis, halothane-treated rabbits displayed antibodies against a set of 5 endogenous antigens and drug-specific antibodies to a number of drugs (including isoniazid and procainamide) were detected in Guinea pigs (upon injection of drug in combination with CFA) (Aida et al., 1998; Katsutani & Shionoya, 1992). With regard to the Guinea pig however, it appeared recently based of FDA records that this species does not provide a reliable predictive animal model (Hastings, 2001).

9.6 Local lymph node assays

Local lymph node assays, such as the LLNA or popliteal lymph node assay (PLNA) are straightforward and robust animal test models that are used to link direct lymph node reactions to local application (epidermal in LLNA, subcutaneously in PLNA) of potentially immuno-active chemicals.

In particular the PLNA has been extensively used to evaluate the potential of certain drugs to stimulate the immune system, and when proper immunologically relevant parameters are assessed the PLNA may also identify immunosensitizing potential (Pieters & Albers, 1999)..

The PLNA is mostly performed in mice (Gleichmann, 1981; Bloksma et al., 1985; Goebel et al., 1996) but also rats (Verdier et al., 1990; Descotes, 1992) have been used basically determines changes in the paw-draining lymph node upon subcutaneous injection of a suspected chemical into footpad. The response, which can be assessed by detecting lymphocyte proliferation, but also by detecting changes in the distribution leukocyte subsets, cytokine production or immunohistology, is determined 6 to 8 days after injection.

Recent modifications include the use of reporter antigens, hence the reporter-antigen PLNA or RA-PLNA (Albers et al., 1997; Gutting et al., 2002a). RA can be regarded as bystander antigens and the response to RA can be determined fairly easily by ELISPOT-assay. Depending on the

antigen used the RA-response provides information about the way the drug stimulates the immune system. For instance, when a compound is co-injected together with TNP-Ficoll, which is a T cell-independent antigen that is susceptible to neo-antigen-specific T cell help, and an increase of TNP-specific antibody forming cells of the IgG isotype is detected it can be concluded that the compound induces T cell sensitization. When using a regular T cell dependent antigen like TNP-OVA chemical-induced increases in the number of TNP-specific IgG-forming cells merely indicate that the chemical has adjuvant activity (providing the response with TNP-Ficoll is negative). So, using immunology based read-out parameters improve the predictability of the PLNA and in addition such parameters allow to further study fundamental aspects of chemical-induced sensitisation (Albers et al., 1997; Gutting et al., 2002a; Goebel et al., 1999; Wulferink et al., 1991; Nierkens et al., 2002).

Up till now, 130-140 compounds (Kammuller et al., 1989b; Albers et al., 1997; Shinkai et al., 1999; Pieters & Albers, 1999; Gutting et al., 1999; Gutting et al., 2002a) including a substantial number of structural homologues of diphenylhydantoin (Kammuller & Seinen, 1988) and zimeldine (Thomas et al., 1989; Thomas et al., 1990), have been tested in the PLNA, and those chemicals with known immunostimulating activity in man were out correctly. However, compounds that require metabolic conversion turned out to be false negative unless metabolic systems (myelin peroxidase (MPO) positive phagocytes, S9 mix) were added as well.

Recently, an inventory study was carried out to evaluate the predictive value of local lymph node approach for the immunosensitizing potential of drugs. Since the footpad injection raises ethical concerns in some instances head-injection and ear-injection with the auricular lymph node as read-out organ were used instead. The head injection protocol showed that of ## the drugs tested were positive and that compounds that were negative mostly were known to require metabolic activation. In a study using the RA-protocol with TNP-Ficoll as RA, ear-injection and subsequent detection of specific antibody formation with a range of pharmaceuticals showed comparable results with the RA-PLNA (Nierkens et al., 2004).

The major drawback route of the PLNA and other local lymph node approaches for drug testing is the route of exposure as most drugs are taken orally. However, the RA approach may also be applicable in combination with oral exposures. It appeared that oral exposure to D-penicillamine, diclofenac or nevirapine for variable periods of time stimulated the DTH and/or antibody

responses to the RA TNP-OVA after 3-4 weeks. Apparently these drugs are capable of adjuvating systemic immune responses to bystander antigens.

In addition, single oral exposures of D-penicillamine (Nierkens et al, 2005, in press) or diclofenac (Gutting et al., 2002b); Nierkens et al, in press) have also been shown to cause chemical specific T cell sensitization. This sensitization could be detected as an increased IgG1 response to TNP-Ficoll in the PLN after challenge of TNP-Ficoll together with subsensitizing doses of the respective drugs in the paw.

9.7 Concluding remarks

Auto-immunogenic and allergenic effects of compounds are usually missed in regulatory toxicity studies, in part because animals that are used are outbred but also because relevant parameters are not detected. In addition outliers are usually discarded from the experiment whereas it are in fact these outliers that may give an indication of unexpected and idiosyncratic immune effects. In addition, although a number of models displaying chemical-induced autoimmunity exist a general model or strategy to assess a the allergenic or autoimmunogenic potential of a wide range of chemicals is lacking.

Because of the idiosyncratic nature of many of the chemical-induced autoimmune diseases, achieving one standard model for the prediction of these side effects might be an illusion. Rather, one might try to design a tool-box approach with a number of models that fit to a two- or multiple-tiered approach. Based on the existing insight that the process leading to hyper-reactivity responses or autoimmune diseases may start in many cases with an initial phase of immunosensitization the first tier may comprise of one of the local lymph node approaches (either or not in combination with a metabolizing system but preferably with an immunological read-out parameter such as the RA approach). This first tier would allow to screen for the worst case hazard of a chemical's potential to stimulate the immune system. In a next tier chemicals that are positive in the PLNA should be further evaluated in suitable (to be developed) animal models (e.g. using autoimmune-prone animals) that use systemic exposure routes (mostly oral) and immunological and preferentially clinical outcomes.

10. HUMAN TESTING FOR AUTOIMMUNE DISEASE

10.1 Introduction

Many hundreds of different autoantibodies have been described to date (Peter & Shoenfeld, 1996). These autoantibodies are most often detected in body fluids that are easily obtained, i.e. in serum or plasma. Therefore, autoantibody assays are primarily standardized for measuring autoantibodies in the circulation. The mere demonstration of autoantibodies is not equivalent to diagnosis of an autoimmune disease. For instance, autoantibodies are relatively common in healthy humans, especially in the elderly. Furthermore, there exist so-called natural autoantibodies, being primarily low affinity IgM antibodies, which may represent a physiologic phenomenon and may even have a protective function. Testing for autoantibodies is most often based on the usage of solid-phase autoantigens (Rose et al., 2002a). After binding of autoantibodies visualization is obtained by subsequent binding of labelled anti-human immunoglobulin reagents. Alternatively, precipitation of antigen-antibody complexes, often facilitated by addition of anti-human immunoglobulin reagents, enables the detection of specific autoantibodies. The current section will primarily discuss the different methods of human autoantibody detection, as well as the implication of the choice of autoantigen preparation and anti-human immunoglobulin reagents for the interpretation of the results obtained. In the context of this EHC document it should be stressed that these tests are designed as diagnostic tests and not for identifying chemical-disease associations per se. Next we will discuss the measurement of immunoglobulin isotypes and subclasses since several autoimmune diseases are characterised by polyclonal B cell activation, resulting in hypergammaglobulinemia. Quantification of subclasses may be especially important because environmental chemicals may result in skewing of the immune response, in particular towards a type-2 cytokine response causing elevated levels of the IgG4 subclass and IgE isotype. Finally, we will allude to experimental methods that are being explored for antigen specific immune responses that are elicited up on chemical exposure. These tests will be mentioned only shortly since they are poorly validated as compared to the diagnostic tests that are in use for human autoimmune diseases.

10.2 Methods of human autoantibody detection

10.2.1 Indirect immunofluorescence technique

The indirect immunofluorescence (IIF) technique is based on the specific binding of circulating autoantibodies to an antigen substrate consisting of tissue sections or cell suspensions. These substrates are attached on a glass slide and are either air-dried or incubated with a fixative to

facilitate autoantibody binding. Next, the non-specific antibodies are washed away, and incubation with an anti-human antibody reagent conjugated to fluorescein isothiocyanate (FITC) enables the visualization of autoantibody binding with the aid of a fluorescent microscope. Knowledge about the tissue distribution or cellular localization of the autoantigen of interest is essential for the proper interpretation and this requires an experienced microscopist. A distinctive reaction pattern will be obtained by the presence of different types of autoantibodies, but the read-out may be hampered by the presence of multiple autoantibodies reacting with different autoantigens in the same tissue. Although computer-assisted classification of immunofluorescent patterns in autoimmune diagnostics is a promising development, further improvement is required for the usage of such a system in routine diagnostics. IIF on tissue sections and cell suspensions (typically Hep-2 cells or neutrophilic granulocytes) is widely used as a screening assay for the presence of autoantibodies in case of organ specific and systemic autoimmune diseases, respectively. The obtained results may require confirmation in antigen-specific assays (vide infra). Quantification of autoantibodies by IIF is at best semi-quantitative. This is most often performed by testing serial, two-step dilutions or, alternatively, by quantitative image analysis of a single dilution of the serum sample. In the latter case the fluorescence intensity obtained with a patient sample is compared to the intensity of standardized calibrators. The fluorescence intensity is directly converted into an antibody titer.

10.2.2 Counter-immuno electrophoresis

The method of counter-immuno electrophoresis (CIE) depends on the formation of immune-complexes in an agarose matrix. Insoluble immune complexes are typically formed at the site where an antibody encounters its antigen in an optimal concentration. Both, excessive antigen concentration, as well as excessive antibody concentration, will prevent immune-complex formation. In case autoantibodies are present in the serum sample a precipitation line will form at the point of equilibrium. In case of CIE the migration of antibody and antigen toward each other is facilitated by addition of an electrolyte to the agarose matrix and applying an electronic current across the gel. Alternatively, antibody and antigen can migrate only because of diffusion; this assay is referred to as Ouchterlony assay. For diagnostic purposes CIE is primarily used for the detection of autoantibodies to extractable nuclear antigens (ENA). These antigens are negatively charged in the electrolyte containing matrix, whereas the autoantibodies are positively charged. Therefore, the former migrate to the anode and the latter reversely towards the cathode. Since thymic extracts of rabbit or bovine origin are used, containing multiple antigens, several different precipitation lines may be obtained in a screening assay in case distinct antibodies are

present in the test serum. Positive samples have to be re-analysed next to antibody preparations of well-defined mono-specificity in alternating wells. In case of identity in the precipitating antigen-antibody combination the immunoprecipitation lines of two neighbouring wells will fuse, whereas non-identical combinations will result in crossing immunoprecipitation lines. It is clear that CIE is only a qualitative screening assay.

10.2.3 Haem-agglutination

Aggregation of red blood cells can be triggered up on cross-linking surface antigens with a specific antibody. This haemagglutination technology is not only fundamental and widely used in blood group serology, but can also be adopted for autoantibody detection to a whole array of antigens. The so-called Coombs test either detects *in vivo* bound autoantibodies (and/or complement) to the surface of the red blood cells (direct Coombs test), or detects and/or types circulating autoantibodies directed to erythrocytes (indirect Coombs test). In case of the direct Coombs test addition of anti-human globulin reagent will directly agglutinate the erythrocytes if autoantibodies (and/or complement) have bound to their surface. The indirect Coombs test is started with incubation of test red blood cells with patient serum prior to incubation with anti-human globulin reagent. To increase the sensitivity of the indirect Coombs test and to detect IgG antibodies it is required to pre-treat the red blood cells by addition of colloid, proteolytic enzymes, or low ionic strength saline. As already mentioned, the antibody detection system is also widely used to determine the presence of other, red blood cell unrelated (auto)antibodies. In these assays the respective autoantigens are bound to the surface of chemically modified erythrocytes. Modification may occur by pre-treatment of the erythrocytes with either tannic acid or chromic chloride. Several of these autoantigen-precoated erythrocytes are commercially available. A difference with the Coombs test is the origin of the red blood cells. To prevent false positive reactions to blood group antigens xenogeneic, for instance chicken or turkey, red blood cells are used instead of human red blood cells in the Coombs test. If autoantibodies are present the antigen-coated red blood cells will agglutinate up on incubation of patient serum. This assay can be performed in serial dilutions in microtiter plates to obtain semi-quantitative results when a reference reagent is included. Actually, any type of antigen-coated microspheres, that precipitate upon cross-linking, can be applied for this type of assay.

10.2.4 Enzyme-linked immuno-sorbent assay/fluorescent enzyme immuno-assay

In the enzyme-linked immunosorbent assay (ELISA) an enzyme is employed which is conjugated either to anti-immunoglobulin reagents or to antigen-specific antibodies. This

immunoassay may detect the presence of antibody or antigen. Furthermore, there exist a multitude of different ELISA systems: direct *vs* capture ELISA's and competitive *vs* non-competitive ELISA's. In general, competitive ELISA's are applied for antigen quantification, while direct, non-competitive ELISA's are the primary method of choice for autoantibody detection. In this latter assay microtiter plates are first coated with the antigen and free binding places are blocked to prevent non-specific binding of antibodies. Next, antigen-specific autoantibodies are enabled to interact with the antigen. After removal of non-specific antibodies in a wash-step, the microwells are incubated with enzyme (horse radish peroxidase or alkaline phosphatase) conjugated anti-human immunoglobulin. In the presence of autoantibodies this will result in the formation of an enzyme-labelled complex of antigen, autoantibody, and anti-human immunoglobulin that converts the finally added substrate to form a coloured end-product. The extend of colour formation is positively correlated with the autoantibody concentration in the test medium. With properly determined cut-off values the ELISA may be applied as a qualitative assay revealing only positive or negative results. The ELISA may even give quantitative results in international units if well defined reference standards are available, or in arbitrary units when other standards are used. Fluorescent enzyme immuno-assays (FEIA) are basically similar to the direct, non-competitive ELISA's. The main difference is that a fluorochrome instead of an enzyme is conjugated to the anti-human immunoglobulin. A prerequisite of direct ELISA's or FEIA's is that the autoantigen can be obtained in great purity since other autoantibodies may react with the contaminants and cause a similar reaction as the autoantibodies to be tested for. Therefore, in case autoantigen purification is hampered in any way, a capture ELISA may be more appropriate. In the capture ELISA an antigen-specific monoclonal antibody is bound to the microwells. Next, the autoantigen will more or less be purified by the capturing antibody and all other contaminants are removed by washing the mircoplates. All further steps are essentially the same as in the direct ELISA. Selection of reagents, however, is more delicate, because the anti-human immunoglobulin should not react directly with the capturing monoclonal antibody. Since the autoantigen is presented in a native orientation, the capture ELISA is more sensitive than the direct ELISA. On the other hand, the epitope recognized by the capturing monoclonal antibody is blocked. This seems to be only a minor disadvantage of the capture ELISA since autoantibody responses are polyclonal and in general directed to multiple epitopes.

10.2.5 Radio-immuno assay

The radio-immuno assay (RIA) is a liquid phase assay in which a radio-labelled antigen is precipitated by the combination of specific autoantibodies and anti-human immunoglobulin. If

the antigen is a receptor (for instance the acetyl-choline receptor), a ligand (i.e. the snake venom α-bungarotoxin), may be radio-labelled in stead of the antigen. The extend of radioactivity in the precipitated immune-complexes is directly related to the autoantibody concentration in the test sample. Like in ELISA/FEIA, the use of well defined international standards enables the generation of quantitative results. This assay specifically detects high affinity antibodies which are considered to be clinically most relevant. This is particularly true in case of detection of anti-double stranded (ds)DNA antibodies by the so-called Farr assay, which is a somewhat modified RIA. On the other hand, the RIA is hampered by the requirement of pure antigen preparations as well as special facilities for working with radioactive material.

10.2.6 Immunoblotting

The immunoblotting procedure is essentially the same as for IIF and ELISA. Proteins are bound to membrane carriers by direct application in dots (dot-blot) or lines (line-blot), or transferred from an electrophoresis gel (Western blot). In case of the dot-blot and line-blot pure antigen preparations are required. Western blotting may apply crude antigen preparations because the antigens are separated by electrophoresis and simultaneous blotting of a molecular weight marker enables the identification of the autoantigen by molecular weight characteristics. Alternatively, a well defined mixture of purified or recombinant antigens may be applied. The latter are often commercially available as prepared membranes. After application of the antigen(s) to the membrane, free binding sites are blocked with an irrelevant antigen to prevent binding of non-specific antibodies. After incubation with the test sample and subsequent removal of non-specific antibodies by a wash procedure, the blot is incubated with anti-human immunoglobulin conjugated to an enzyme. Incubation with an appropriate substrate will result in an insoluble, detectable reaction product at the site where autoantibodies have bound to their respective antigens. Alternatively, fluorochrome or radioactive labels can be applied. Obviously, blotting procedures will give only qualitative results as in CIE. Additionally, however, Western blotting enables determination of the molecular weight of the recognized antigen and as such gives an extra indication to the antigen-specificity. A disadvantage of the Western blotting approach is that the proteins are separated by gel-electrophoresis in the presence of SDS, resulting in partial denaturation of the proteins and subsequent loss of antigenic epitopes.

10.2.7 Multiplex analysis

Whereas in immunoblotting, and to a lesser extend also in IIF, several autoantibodies can be detected in qualitative terms in one single test, there is progression towards quantitative detection

of multiple autoantibodies in a single fluorescent-based assay. This so-called multiplex immunoassay is based on a mixture of bead subsets that are each labelled with a unique combination of internal fluorescent signal and antigen. In essence, each bead subset represents a separate immunoassay, but due to the distinct internal fluorescent signals many combinations of these assays can be analysed in the same tube. Incubation with the serum sample enables binding of autoantibodies to the beads labelled with the respective antigens. Like in other assays, the non-specific antibodies are washed away. After incubation with fluorescent anti-human immunoglobulins the presence of autoantibodies can be detected by flow cytometry. Autoantibodies can be quantitated from standard curves obtained by measuring the signal intensity of beads coated with well-defined amounts of antigens. One disadvantge of this assay is that, depending on the complexity, it may generate positive results that have not been asked for by the clinician. The laboratory should determine in advance how to cope with this type of results.

10.3 Selection of detection method

Since the different methods for autoantibody detection as described above differ in terms of laboratory requirements, the local situation influences the choice of method. For instance, RIA and multiplex analysis require investments in special facilities and equipment. IFT and, to a lesser extend, immunoblotting require less investments but demand the availability of properly trained technicians. Also the results obtained are different in terms of qualitative versus quantitative data and in terms of the immunoglobulin isotype that is recognized by the anti-human immunoglobulin reagent. This type of differences will have an impact on the clinical applicability. Finally, the selection of methods is restricted by the availability of highly purified or recombinant antigens since several assays (haemagglutination, direct ELISA, FEIA, RIA, and multiplex analysis) can not be employed with crude antigen extracts.

10.3.1 Autoantigens

The autoantigen used in a test can be of different quality: purified or present in a whole mixture of antigens, native or recombinant, and of human or animal origin. Antibodies tend to recognize conformational epitopes and therefore the three-dimensional structure of the autoantigen, and in some instances the non-covalent interaction with associated molecules, should be maintained. Obviously, post-translational modifications will be detrimental to the structural organization of the protein. Therefore, the choice of autoantigen will directly influence basic characteristics, like sensitivity and specificity (vide infra), of the test system. In particular IIF, when applied on

human cells or tissues, has an optimal source of autoantigen being species specific, native in origin, and unmodified by isolation procedures. However, in many instances the structure of the autoantigen is affected by fixation of the tissue/cells. Furthermore, due to many legal regulations and risks of infections, it becomes more and more difficult to obtain human tissue for IIF. Therefore primate tissues, with almost similar restrictions as human tissues, or even rodent tissues are widely used. It may be clear that this will reduce the sensitivity of the assay. Mixtures of autoantigens, present in crude extracts, are also used in the CIE and Western blotting. In these cases the three-dimensional structure of the autoantigen may be affected during electrophoresis by the electrolytes and the denaturing conditions, respectively. All other assays utilize purified or recombinant autoantigens. Impurity of the autoantigen preparation is a critical caveat in most assays, but not in the capture ELISA and the Western blot. In the first assay further purification is achieved during the capturing step with the antigen-specific monoclonal antibody, in the latter assay the molecular weight of the recognized antigen will enable distinction between autoantigen and contamination, unless of (nearly) similar molecular weight. Recombinant protein technology has provided an alternative to circumvent problems with purification (Schmitt & Papisch, 2002). Reombinant proteins can be species specific and obtained in large and pure preparations. Although purification from the expression system, like *E. coli,* yeast or baculovirus in insect cells, is still required, the purification can be facilitated by cloning a special tag at the end of the recombinant protein. Nevertheless, depending on the applied expression system, the use of recombinant autoantigens is hampered by differences in post-translational modifications and therefore may result in reduced sensitivity. In the future this problem may be overcome by co-expression of the relevant processing factors in the expression system.

10.3.2 Anti-immunoglobulin reagents

Anti-human immunoglobulin reagents are required in most, but not all (CIE, haemagglutination), immunoassays for the detection of autoantibodies. There exists a wide array of anti-human immunoglobulin reagents and conjugated reporter molecules. The proper choice is relevant in terms of clinical interpretation of the obtained results. Anti-immunoglobulin reagents may react with all immunoglobulins, with specific isotypes, or even with subclasses. In many autoimmune diseases the detection of distinct immunoglobulin isotypes is not of equal importance. Overall, autoantibodies of the IgM isotype are diagnostically less specific for autoimmune diseases since these IgM autoantibodies are typically of low affinity and represent the so-called natural autoantibodies. Some exceptions of this rule include IgM rheumatoid factor and high titer IgM anti-cardiolipin antibodies. The first of these two, the IgM rheumatoid factor, may even cause

false-positive results for other IgM autoantibodies since these antibodies may interact with the Fc-chain of an IgG autoantibody and thereby mimic an IgM response. Isotype switching from IgM to IgG or IgA indicates the involvement of T cells which is considered a hallmark of autoimmune disease. IgA autoantibodies are particularly relevant for autoimmune diseases that affect mucosal tissues; in most other instances autoantibodies of the IgG isotype are most specific. The quality of the isotype-specific anti-human immunoglobulins is quite diverse. While domestic animals are immunized with purified immunoglobulin isotypes, the obtained anti-human immunoglobulin reagents are not isotype-specific. Due to the presence of light chains common to all immunoglobulin isotypes, antibody responses to these light chains will react with all immunoglobulin isotypes. Therefore, further processing of the obtained antisera is required and this includes depletion of the anti-immunoglobulin antibodies that react with the light chains. Besides the generation of anti-human immunoglobulin reagents in other species, there also exist naturally occurring molecules with the intrinsic capacity to specifically interact with human IgG, for instance the *Staphylococcus aureus* cell wall protein A or the group G *Streptococcus* cell wall constituent protein G. Both reagents differ in terms of human IgG subclass detection: whereas protein G recognizes all four IgG subclasses, protein A does not recognize the IgG3 subclass. The issues discussed above mainly affect the specificity and clinical relevance of the results obtained. Another part of the anti-human immunoglobulin reagent is the reporter molecule that is conjugated to it. These reporter molecules include enzymes or fluorochromes, and exceptionally radioactive markers. These reporter systems differ in assay sensitivity. Even higher assay sensitivities can be obtained by conjugation of for instance biotin and subsequent incubation with streptavidin conjugated with any type of reporter molecule. In general, these highly sensitive approaches are not required for the detection of human autoantibodies.

10.4 Clinical interpretation

The goal of a diagnostic test is to distinguish between individuals with and without a particular disease. Several confounding factors may hamper the correct interpretation of test results. The variability of the test should be small compared to the reference interval or range of normal. Thus, the test has to be accurate and precise. Bias can occur due to variation in the studied subject, instrument or observer. The applicability of a test rests on its comparison with the “gold standard”, which discriminates between individuals who certainly have and those who do not have the disease. Several parameters are in use which determine the value of a test result. The most commonly used parameters are sensitivity and specificity (Box 1), which both, in the gold standard, by definition are 100%. Sensitivity is defined as the probability of a positive test result

in a patient with the disease under investigation. Specificity is the probability of a negative test result in a patient without the disease under investigation. Whether a test result is positive or negative is dependent on the cut-off point of the assay. In order to pinpoint the cut-off point that results in optimal sensitivity and specificity a receiver operating characteristic (ROC) curve can be generated by plotting sensitivity vs. 1-specificity. Overall, the best cut-off maximizes the sum of sensitivity and specificity, which is the point nearest the top left-hand quadrant. However, depending on whether test results are used to detect or exclude a disease, for monitoring exacerbations of a disease, or for population screening, different cut-off points may be optimal.

It is of great practical concern to know the predictive value of positive and negative test results, that is the proportion of those with a positive test who actually have the disease, and the proportion of those with a negative test who actually do not have the disease, respectively (Box 1). These values strongly depend on the true prevalence of the disease under study. Likelihood ratios (LRs), on the other hand, indicate the proportion of individuals with and without the disorder at a given level of a diagnostic test (Box 1). Since the LRs are calculated as a ratio of probabilities, they are not influenced by disease prevalence. Furthermore, LRs can be used in a Bayesian context to generate a post-test probability of disease. Finally, it is important to realize that the variability of the reported values for test systems can differ because a variable amount of healthy controls, and/or relevant disease controls are included in the different studies. Therefore, values given in the literature or by the manufacturer of commercial kits should be interpreted in this context and all laboratories should be recommended to determine their own test characteristics.

Two other test parameters that are important for interpretation of results are the intra- and inter-assay variation. These parameters give information on the reproducibility and reliability of the results. The intra-assay variation is determined by running multiple preparations (5 or more) from the same test sample in the same assay. The intra-assay variation can be calculated as the ratio of the standard deviation and the mean, and is expressed as percentage after multiplying

the ratio by 100. The inter-assay variation is determined by running the same test sample in multiple, consecutive assays (5 or more). The formula for calculating the inter-assay variation is similar to the one for calculating the intra-assay variation. Preferentially these variations are determined in samples with low, medium, and high values. In general the inter-assay variation is

higher than the intra-assay variation. Therefore, in case of high inter-assay variation, it is recommended to run consecutive follow-up samples in the same assay in order to obtain reliable changes in autoantibody titers.

Box 1: Formulae of test parameters

		Disease:	
		Present	Absent
Test:	Positive	True Positive **(A)**	False Positive **(B)**
	Négative	False Negative **(C)**	True Negative **(D)**

$$\text{Sensitivity} = \frac{\text{true positive}}{\text{true positive} + \text{false negative}} = \frac{A}{A + C}$$

$$\text{Specificity} = \frac{\text{true negative}}{\text{false positive} + \text{true negative}} = \frac{D}{B + D}$$

$$\text{Positive predictive value} = \frac{\text{true positive}}{\text{true positive} + \text{false positive}} = \frac{A}{A + B}$$

$$= \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$$

$$\text{Negative predictive value} = \frac{\text{true negative}}{\text{false negative} + \text{true negative}} = \frac{D}{C + D}$$

$$= \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity}) \times (1 - \text{prevalence})}$$

$$\text{Positive likelihood ratio} = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{A/(A + C)}{B/(B + D)}$$

$$\text{Negative likelihood ratio} = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{C/(A + C)}{D/(B + D)}$$

10.5 Human immunoglobulins

10.5.1 Autoimmune disease and human immunoglobulin levels

In general, all immunoglobulin isotypes and subclasses can be detected in the human circulation. Since antibody production is the consequence of immune stimulation it is evident that immunoglobulin levels increase during childhood and reach relatively stable levels during adulthood. Chronic immune stimulation, as is the case in autoimmune diseases, may result in further elevation of immunoglobulin levels, i.e. hypergammaglobulinemia. These increases in immunoglobulins may even be isotype specific. For instance, hyper-IgG levels are observed in systemic lupus erythematis and autoimmune hepatitis, while hyper-IgM levels are characteristic for primary biliary cholangitis. However, not only increased antibody concentrations are associated with autoimmune diseases, also antibody deficiencies may be associated with an increased prevalence of autoimmune diseases. This is particularly evident in case of selective IgA deficiency which is observed in 5-10% of patients with celiac disease, while the prevalence of IgA deficiency in the healthy population is only 1:800. For these reasons several autoimmune diseases have a diagnostic indication for evaluating the immunoglobulin levels in the circulation. Furthermore, antibody quantification may also give a clue to the skewing of the immune system towards type-1 or type-2 cytokine production, i.e. pro- and anti-inflammatory cytokines, respectively. In particular IgG subclasses and IgE responses are helpful in this respect: production of IgG1 and IgG3 are associated with type-1 cytokine responses, while IgG4 and IgE are associated with type-2 cytokine responses. This distinction is probably most apparent in the detection of anti-cardiolipin antibodies. These antibodies are a hallmark of the anti-phospholipid syndrome and in particular the IgG2 and IgG4 subclasses are associated with clinical manifestation of APS. Anti-cardiolipin antibodies of the IgG1 and IgG3 subclasses, on the other hand, are induced by infections and appear not to be involved in the immunopathogenesis of APS. Moreover, elevated IgG4 and IgE levels are induced upon contact with several environmental factors, like mercury- and gold-salts.

10.5.2 Quantification of human immunoglobulins

Many different immunoassays can be used for the quantification of immunoglobulin isotypes and subclasses, varying from ELISA/FEIA, radial immuno-diffusion, to nephelometry/turbidimetry (Rose et al., 2002). Especially the immunoglobulin isotypes IgA, IgG, and IgM are present in relatively high concentrations in the circulations (0.5 – 20 g/L). These isotypes are often quantified by nephelometry/turbidimetry. Since the concentrations of

IgD and IgE are much lower (IgD: 0.04 g/L; IgE: $3x10^{-5}$ g/L), more sensitive assay methods are required for the detection of these latter two isotypes.

Nephelometry and turbidimetry are based on the formation of immune complexes in solution and the subsequent effect on light scattering of incident light. The basic principles of light scattering by particles is beyond the scope of this discussion. The formation of immune complexes is accomplished by the addition of an optimised dilution of specific antiserum to a dilute antigen solution resulting in more or less equivalent presence of antigen and antibody. As already stated, immune complex formation is prevented in situations of antigen excess or antibody excess. The newly formed immune complexes will scatter light from an incident light beam. In case of nephelometry increased side scattering at an angle to the incident light beam is determined, while in case of turbidimetry the loss in light intensity passing straight forward through the solution, due to side scattering, is measured. Some automates combine both detection principles for calculating antigen concentrations. As mentioned above, these techniques are very suitable for quantifying the immunoglobulin isotypes IgA, IgG, and IgM. The IgG subclasses, in particular IgG3 and IgG4, are present in the circulation in relatively low concentrations. They can be quantified by nephelometry/turbidimetry if the immune complex formation is enhanced. This is achieved by coupling the specific antiserum to, for instance, latex particles. In any case, quantitative results are obtained by relating the signal of the test sample to calibrators that have assigned values for the antigen of interest.

The radial immuno diffusion (RID) or Mancini assay is also based on the formation of immune complexes. This occurs in an agarose matrix containing the specific antiserum. The antigen is applied into a small hole in the matrix and disperses through this matrix due to diffusion. As soon as equivalent concentrations of antigen and antibody are reached, the molecules will precipitate revealing a precipitin ring. There is a linear relationship between the antigen concentration and the squares of the ring diameters (endpoint method), or between the log of the antigen concentration and the ring diameters (timed-diffusion method). The use of appropriate calibrators enables quantification of results. This technique is often applied for the detection of IgG subclasses and IgD concentrations.

Finally, the extremely low IgE concentration in the circulation requires very sensitive detection methods, i.e. ELISA/FEIA, RIA, or modifications of these methods. Basically, these techniques are similar as described for the detection of autoantibodies. In case of ELISA/FEIA it concerns a

capture technique where the IgE molecule is first captured by an anti-IgE monoclonal antibody and subsequently recognized by an enzyme/fluorochrome-conjugated anti-IgE monoclonal antibody.

10.6 Testing in the diagnosis of delayed-type chemical hypersensitivity

Delayed-type chemical hypersensitivities can be subdivided into two subgroups, which differ in their pathophysiology: 1. immune responses directed to the chemical itself, a metabolite of the chemical, or some contamination of it, and 2. autoimmune reactions, in which the chemical elicits an immune reaction to autologous structures. Diagnosis of chemical hypersensitivity is difficult, as an enormous amount of different chemicals can elicit various immune-mediated diseases with distinct mechanisms. The diagnosis is mainly based upon a very detailed history and the clinical findings. In addition, several *in vitro* or *in vivo* tests, like skin tests, serological tests, and the lymphocyte transformation test (LTT), can be performed to demonstrate a sensitisation to a certain chemical (Choquet-Kastylevsky et al., 2001; Pichler, 2003).

Skin testing is based on the application of chemical solutions on the epidermis, with (scratch-patch test) or without (patch test) scarification of the epidermis. The occurrence of a typical type IV hypersensitivity reaction, i.e. erythema, vesiculation, and evidence of cellular infiltrate, 48 to 96 hours after application is typical for a positive reaction. Topical chemical application, usually on the upper and mid zone of the back, is performed to avoid the risks of systemic rechallenge. A drawback of this approach is that the metabolism of the chemical, leading to the generation of a reactive metabolite, and the presentation of the chemical to the immune system may be different according to the route of entry. Other limitations to the interpretation of *in vivo* tests are that co-factors of critical importance may be absent when the test is performed or that the test may be performed too early after the adverse chemical reaction while the immune system may still be in a refractory state. It is therefore recommended to perform skin tests within 6-12 weeks after the occurrence of the adverse chemical reaction.

In vitro testing of delayed-type chemical hypersensitivity is based on the detection of chemical-specific IgG antibodies and/or T-cells. chemical-specific IgG antibodies are detected in solid phase assays where the chemical is bound to various carriers like nitrocellulose or sepharose. These methods are controversial and are not recommended for the routine diagnosis of chemical hypersensitivity. Chemical-specific T-cell responses are measured in the so-called LTT. This test reveals a sensitisation of T-cells by an enhanced proliferative response of peripheral blood mononuclear cells to a certain chemical. Generally, lymphocyte transformation is measured by

^{3}H-thymidine incorporation into DNA, but alternative, flow cytometry-based methods are available as well. Although this test can be a useful tool for clinical diagnosis, a positive LTT can only signal a previous contact with the respective chemical and is not specific for delayed-type hypersensitivity. Furthermore, *in vitro* testing precludes the generation of reactive metabolites, which may contain the actually involved antigen.

Altogether, accurate and reliable diagnostic tests for the evaluation of adverse chemical reactions remain problematic. At the present time, none of these tests has been properly validated as a specific and sensitive diagnostic tool of delayed-type chemical hypersensitivity. Moreover, these tests only enable immune reactivity to the chemical itself: in cases where the chemical elicits an immune reaction to autologous antigens, conventional methods for the diagnosis of autoimmune diseases, as discussed in the first part of this chapter, are more appropriate. Table 14 lists a broad panel of laboratory tests (general and immunological) to enable detection of a variety of abnormalities associated with induction of autoimmunity that may occur after environmental chemical exposure. Obviously, this screening panel should be done in conjunction with clinical evaluation since positive results in laboratory testing do not make a diagnosis or predict the subsequent development of autoimmune disease. Further, more specific testing should be done to aid in the diagnosis of possible autoimmune disease.

10.7 Conclusions

Exposure to chemicals may have a strong impact on the immune system: chemicals or its metabolites may be inert, may induce a delayed-type hypersensitivity reaction to the chemical, or may even break tolerance due to conjugation with auto-antigens and revealing neo-epitopes. Additionally, chemicals may induce changes in the balance between type-1 and type-2 immune responses. There exist a great variety of methods for monitoring these potential, chemical-mediated effects. In contrast to the diagnostic test systems for autoantibody detection, the tests available for measuring immunity to chemicals that may cause delayed-type hypersensitivity reactions are only poorly validated for clinical purposes. Furthermore, these tests only assess immune reactivity to the chemical itself and do not measure autoimmunity. With respect to autoantibody testing, several health organizations have proposed a testing scheme for preliminary evaluation of individuals exposed to chemicals (IPCS, 1996). The World Health Organization (WHO) suggests testing for anti-nuclear antibodies, anti-dsDNA antibodies, anti-mitochondrial antibodies and rheumatoid factor. The screening panel recommended by the United States Centers for Disease Control and Agency for Toxic Substances and Disease

Registry include anti-nuclear antibodies, rheumatoid factor, and anti-thyroglobulin antibodies, whereas the United Stated National Academy of Sciences recommended beside the tests suggested by the WHO, also antibodies to red blood cells. However, no advises with regard to the method of detecting these autoantibodies and relevant cut-off values are given and, as stated in this chapter, this may influence the conclusions drawn from the results obtained.

Table 14: Laboratory tests for the assessment of abnormalities associated with induction of autoimmunity related to environmental chemical exposure

General Laboratory Tests:

These tests will provide basic information about health abnormalities.

- Complete blood count (white and red blood cell counts, differential leukocyte counts, thrombocyte counts, hemoglobin concentration, haematocrit, red cell indices) will provide information on hematological status and inflammatory conditions.
- Urinanalysis (glucose, protein, hemoglobin by dipstick; if positive, specimen should be centrifuged and the pellet examined for red blood cells and casts) should be done to detect kidney dysfunction and/or diabetes.
- Clinical chemistry (ALT and AST as markers of liver damage, CPK for muscle damage, creatinine for kidney dysfunction. C-reactive protein will point at an acute phase response (inflammation).
- T3/T4 or TSH will indicate thyroid dysfunction.

Immunological Laboratory Tests:

These tests will provide more specific information about immune dysregulation and autoimmune reactions.

- Immunoglobulin levels (IgG, IgA, IgM) should be used for detection of polyclonal stimulation. For example polyclonal elevations of IgG levels can be a characteristic of SLE or Sjögren's syndrome. IgE and/or subclasses of IgG should be determined as an indication of changes in the Th1/Th2 balance.
- Autoantibodies:
  1. Antinuclear antibodies (by IIF). If ANA by IIF is positive, specificity of the ANA should be determined. ANA specificities associated with the development of systemic autoimmune diseases are: autoantibodies against dsDNA, nucleosomes, histones, Ro/SS-A, La/SS-B, U1-RNP, Sm, DNA-Topoisomerase I (Scl-70), centromere protein, and Jo-1.
  2. Anti-neutrophil cytoplasmic antibodies (by ELISA for MPO-ANCA and PR3-ANCA or by IIF on normal neutrophils). ANCA are markers for the small-vessel vasculitides, like Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome.
  3. Rheumatoid factor (by ELISA or, if ELISA testing is not available, by particle agglutination). RF refers primarily to the IgM antibody which binds aggregated IgG as its antigen. RF is associated with rheumatoid arthritis.
  4. Organ-specific antibodies, like anti-thyroid (peroxidase) for detection of thyroid specific autoimmunity. Other organ specific autoantibodies may also be selected if organ-specific autoimmune reactions are expected.

  Interpretation of the tests for autoantibodies will depend on the class and titre of the antibody and the age and sex of the test subject. Autoantibodies can be found in normal, healthy individuals, especially elderly females.

List of abbreviations

CIE	counter-immuno electrophoresis
ds	double-stranded
ELISA	enzyme-linked immunosorbent assay
ENA	extractable nuclear antigens
FEIA	fluorescent-enzyme immuno-assay
FITC	fluorescein isothiocyanate
IIF	indirect immunofluorescence
LR	likelihood ratio
LTT	lymphocyte transformation test
RIA	radio-immuno assay
RID	radial immuno diffusion
ROC	receiver operating characteristics
WHO	World Health Organization

11. RISK ASSESSMENT

11.1 Introduction

Chemicals and drugs used for a variety of purposes can have adverse effects on the immune system. One form of immunotoxicity is the direct toxicity of the compound to components of the immune system, which may lead to suppressed function. A second type of immunotoxicity is allergy in which the compound causes the immune system to respond as if the compound were an antigen. Autoimmunity that may lead to the development of autoimmune disease (AID) represents a third type of adverse effect where the exposure to certain chemicals or drugs may play an important role. Autoimmunity is characterized by the reaction of cells (autoreactive T lymphocytes) or products (autoantibodies) of the immune system against the organism's own antigens (autoantigens). Autoimmunity may be part of the physiological immune response or pathologically induced with development of clinical abnormalities, the autoimmune diseases. AID are characterized by an inappropriate or excessive immune response leading to chronic inflammation, tissue destruction and/or dysfunction.

11.2 Prevalence of autoimmune diseases

Generally, AID are perceived to be rare, but when all AID are combined the estimated prevalence of 3-5% is not rare and underlies the importance in the public health sector. Because of problems in designing and standardizing epidemiological studies and because of limited data that are available, this prevalence may be underestimated. There is epidemiological evidence of increasing prevalence of AID in the Western countries not only due to better diagnostics (Jacobson et al., 1997). Moreover, more and more diseases are classified as autoimmune when less criteria compared to classic AID are fulfilled. Furthermore, there is growing evidence that autoimmune mechanisms may play a (secondary) role in many other diseases (in up to 20% of all diseases such as atherosclerosis). To date more than 60 diseases have a proven or strongly suspected autoimmune aetiology. It remains a matter of debate how to prove that a given disease is indeed an autoimmune disease. Thus, there is a broad range of diseases with autoimmune pathology ranging from definite AID to diseases in which autoimmunity plays a secondary role.

11.3 Immune mechanisms

Currently, the ethiologies and mechanisms involved in the development of AID are incompletely understood. A multifactorial genesis including immunological, genetic, endocrine and environmental factors is suggested by evidence from both human and animal studies.

Environmental factors (that include chemicals, novel components in food and drugs) operating in a genetically susceptible host may directly initiate, facilitate or exacerbate the pathological immune process, induce mutations in genes coding for immunoregulatory factors, or modify immune tolerance, regulatory and immune effector pathways. Of these environmental factors drug-induced autoimmune disorders and hypersensitivity reactions are a major concern, and often the reason for withdrawing drugs from the market or restricting their use. Mechanisms that apply for systemic allergy symptoms may to a large extent resemble autoimmune-like phenomena, and that only the antigens recognized are different: i.e. in systemic allergy lymphocytes specifically recognize the chemical itself whereas in case of autoimmunity self antigens are recognized. Allergic compounds may induce the release of neoantigens (cryptic epitopes) or alter self-antigen so that they appear foreign. In addition, specificity of an immune response induced by a compound may be initially directed exclusively to the compound but after certain time spread to include auto-antigen directed responses. This process, referred to as epitope or determinant spreading, may explain why after a certain period of exposure allergic patients may also respond to auto-antigens, and end up displaying a mixed allergic-autoimmune response. In this context, it is also important to realize that normal healthy individual possess autoreactive T and B cells to provide a necessary and protective immunological homeostasis. Thus, in the investigation of the possible mechanisms of chemical induced autoimmunity it is important to consider results of studies with allergenic compounds as well.

Immune responses are often categorized according to Gell and Coombs' classification. This categorization into four classical types of hypersensitivity responses does however not hold any longer with regard to drug-induced allergic and autoimmune-like phenomena. For instance with regard to Type IV delayed type hypersensitivity reactions, a revision has been proposed to include other T cell mediated clinical symptoms such as exanthema with eosinophilia. In addition some drugs may induce adverse immune effects without immunosensitization, these immune effects are collectively designated as pseudo-allergic reactions. Also, one drug often elicits a wide range of systemic pathological effects that can be linked to more than one of the four classical types of hypersensitivity responses. The fact that certain chemicals induce a variety of hypersensitivity reactions may indicate that they affect the immune system at more than one particular stage, which has important implications for understanding the mechanisms.

11.4 Structure-activity relationships

The considerable amount of data generated to basic mechanisms of chemical-induced autoimmune diseases have provided a conceptual framework that allows the establishment of potential structure-activity relationships (SARs) (reviewed by Luster et al., 1999; Table 15). These relationships are supported by basic understanding of immunologic and pharmacologic processes. For example, estrogens are known to be a major factor in classic autoimmune diseases, presumably because of their ability to stimulate certain components of the immune system. Laboratory studies have shown that thymolytic chemicals can induce autoimmunity when given neonatally by altering normal patterns of autoreactive T-cell deletion, a process that occurs in the thymus early in life. Chemicals that form protein adducts or damage tissue in such a way to allow expression of cryptic determinants would provide novel host antigens that could be recognized by T cells. Agents that have adjuvant activity or biologicals that stimulate certain cytokines may shift the balance of T-helper 1 and T-helper 2 cells and allow exacerbation of preexisting autoimmune disease. Common features associated with many drugs that induce autoimmune diseases are that they serve as myeloperoxidase substrates and/or cause changes in methylation. The underlying biology for the latter associations are less clear but may involve formation of the specific antigenic epitopes responsible for the autoimmune response. With regard to the association with myeloperoxidase substrates, it has been suggested that many of the chemicals require metabolism in proximity to immune cells in order to be antigenic; immune cells such as monocytes contain high levels of myeloperoxidase.

Table 15: Structure-activity relationships of potential interest[a]

Activity	Chemical example
Thymolytic	Cyclosporin A, cyclophosphamide
Formation of protein adducts	Halothane
Altered immune regulation	Mercury, interferon-γ
Myeloperoxidase substrates	Procainamide
Altered methylation	Hydralazine

[a] from: Luster et al (1999)

11.5 Animal models to assess chemical induced autoimmunity

There are many examples of animal models of chemically induced autoimmune disease. However, whether an autoimmune response occurs in animals upon chemical exposure depends on many factors, including species and strains. Animal species that have been documented to show autoimmune disease-related effects to one or another chemical include the mouse, rat, guinea pig, cat, dog, chicken and monkey. But even the species or strain is sensitive it often takes several months of exposure before autoimmune effects become apparent. And still, for most chemicals, in particular pharmaceuticals, it appears impossible to induce the same adverse immune effects in animals as observed in humans.

11.5.1 Dose-regimen and immunoregulation

Remarkably, chemically induced autoimmune diseases are often transient and resolve spontaneously and can not be induced again in the same animal, e.g. HgCl2-induced autoimmune glomerulonephritis in BN rats. In addition, low dose pretreatment of BN rats with HgCl2 prevents development of adverse immunity. Both phenomena, transience of autoimmune effects as well as low-dose protection, may be due to the development of regulatory immune cells. These findings demonstrate the importance of using a proper dose-regimen.

11.5.2 Genetics and immunoregulation

The genotype of the species or strain is important not only for the occurrence of disease but also for the type of immune effect. This is also apparent from studies on HgCl2-induced autoimmunity. In contrast to BN rats, Lewis rats are resistant to HgCl2-induced autoimmunity but instead demonstrate an overall state of immunosuppression, mediated by suppressor T cells. This suppression is not antigen-specific as HgCl2-treated Lewis rats are also protected against experimental autoimmune encephalitis (EAE). Both MHC and non-MHC genes are involved in the susceptibility to develop AID.

11.6 Induced and genetic models

Chemicals may exacerbate autoimmunity in genetically predisposed animals or in induced animal models. The rationale behind using autoimmune-prone animal strains for the purpose of prediction of autoimmunogenic potential of chemicals is that, apart from being probably very sensitive for adverse immune effects, exacerbation of disease is considered one of the possibilities by which chemicals may elicit autoimmune phenomena. In induced models, a susceptible animal strain is immunized with a mixture of an adjuvant and an autoantigen isolated

from the target organ. Examples are adjuvant arthritis, experimental encephalomyelitis and experimental uveitis in the Lewis strain rat. Examples of spontaneous models of autoimmune disease are the BB-rat and the NOD-mouse that develop autoimmune pancreatitis and subsequently diabetes, and the (NZBxNZW)F1 mouse or MRL/lpr mouse that develop pathology that resembles human systemic lupus erythematosus. Also the BN rat can be regarded as genetically predisposed strain of rat because it responds to many chemicals with an exclusive Th2-response.

11.7 Predictive models for autoimmunity and hypersensitivity

Auto-immunogenic and allergenic effects of compounds are usually missed in regulatory repeated-dose oral toxicity studies, the main reason being the complexity of the process involved (as discussed above for HgCl2) which could make it even impossible to develop a generally applicable animal model or strategy to predict or study adverse effects of chemicals based on clinical effects as outcome parameter.

However, a good candidate for a more generally applicable predictive animals model might be the popliteal lymph node assay (PLNA), mainly because this assay focuses on direct immunostimulation or -sensitization and not on clinical effects as outcome. As a consequence the PLNA in its various forms avoids interference of immunoregulatory processes and allows fast screening of chemicals for possible adverse autoimmune effects.

11.7.1 Primary PLNA and secondary and adoptive PLNA

The primary test, in which lymph node weight, cell number or proliferation of lymph node cells is used as measure for immunostimulation, is a straightforward robust animal model that allows screening of immunostimulatory or sensitizing potential of an array of (structurally or functionally related) compounds. The PLNA is conducted mostly in the mouse and occasionally in the rat. In the secondary PLNA pre-treated animals are re-exposed to the same chemical or a metabolite in a dose that in itself is incapable of stimulating naive T cells. A response measured to this low dose strongly indicates, but does not formally proof, that memory T cell are present. Proof for the formation of memory T cells can be obtained with the adoptive transfer PLNA in which purified T cells obtained from systemically treated mice are transferred to naive recipients that subsequently receive an injection into the paw of a non-sensitizing dose of the same chemical or a relevant metabolite.

11.7.2 Reporter antigen PLNA

In this assay, the antibody response to a co-injected reporter antigen (RA) is used as read-out parameter. The reporter antigens TNP-Ficoll and TNP-Ovalbumin require different circumstances to mount a TNP-specific antibody response. TNP-Ficoll is a sugar-like antigen that can not be presented to and hence recognized by T cells by MHC molecules. TNP-Ficoll is very well capable of directly stimulating B cells to produce IgM isotypes, but this RA is unable to induced other isotypes (e,g IgG) by itself. But B cells responding to TNP-Ficoll are susceptible for soluble non-cognate T cell help. This implies that an increase in TNP-specific IgG may indicate that non-TNP-specific T cell help is provided. These non-TNP-specific T cells may therefore recognize a chemically induced neo-antigen, which can be either a hapten-carrier complex or a cryptic epitope. Hence, a TNP-specific IgG response to TNP-Ficoll is indicative of T cell sensitization. With the RA-PLNA potentially immunosensitizing compounds (positive IgG response to both TNP-Ficoll and TNP-Ovalbumin), can be distinguished from compounds that only cause an inflammatory response and do not stimulate neo-antigen-specific T cells (positive response to TNP-Ovalbumin but not to TNP-Ficoll).

Presently, around 130 compounds have been tested, predominantly in the primary PLNA (Pieters & Albers, 1999}. For those chemicals with known adverse immne effects PLN-responses show a good correlation with the reported ability of a compound to induce AID or contact dermatitis in man. Importantly, if metabolism is considered no false negatives are found. Thus, the direct PLNA seems to be a versatile tool to recognize T-cell activating drugs and chemicals, including autoimmunogenic chemicals, keeping in mind possible false-negative results with prohaptens.

Interestingly, the PLNA technique can be used in combination with relevant route of exposure models. Basically, local assessment of T cell activation in the popliteal lymph node in response to a subcutaneously injected non-immunogenic dose of an appropriate chemical (a hapten, relevant metabolite, native autoantigen or a reporter antigen) may assess the presence of systemic T cell memory and hence systemic immunosensitization in animals that have been exposed to the chemical for a certain period. For example, by combining oral exposure to diclofenac with the RA-PLNA with TNP-Ficoll as read-out method Gutting et al. (2002b) reported that a single oral dose of diclofenac resulted in an increased IgG1 response to TNP-Ficoll when co-injected in the paw with a non-sensitizing dose of the drug, indicating that oral exposure to the diclofenac causes compound-specific T cell memory.

11.8 Testing strategy

Although a number of models displaying chemical-induced autoimmunity exist a general model or strategy to assess a chemical's potential to cause systemic allergy or autoimmune-like adverse effects is lacking. Based on existing insight that the process leading to systemic hypersensitization may start in many cases with an intitial phase of immunostimulation, a two-tiered strategy may be used. In the first tier, the PLNA (either or not in combination with a metabolizing system and/or reporter antigen) can be used to detect the worst case hazard of a chemical's potential to stimulate the immune system.

In the second tier, chemicals that are positive in the PLNA should then be examined in suitable animal models that use systemic exposure routes (mostly oral) and clinical outcome to further assess autoimmunogenic potential. In this, high priority has to be given to the validation of the PLNA and the further development of predictive animal assays. It is important to note that the PLNA in any of its forms is a hazard identification test and belongs to the qualitative stage of the risk assessment paradigm. Because of the lack of suitable and validated animal models, including models to quantify acceptable levels of exposure, the potential risk for inducing autoimmunity cannot be predicted at present. As regulatory guidance is following science, such guidance for autoimmunity is not available.

12 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. Autoimmune diseases are an important health problem, affecting 3-5% of the population. Furthermore, autoimmune mechanisms play a role in many other diseases, hence more than these 3-5% will encounter autoimmune-associated health effects.

2. The information yielded by epidemiology studies pertaining to chemical-induced autoimmunity are hampered because of problems in designing and standardizing such studies. The current figures on prevalence may actually be underestimated. There is epidemiological evidence of increasing prevalence of AID in the Western countries, which cannot be attributed to better diagnostics alone.

3. Autoimmunity and autoimmune diseases concequences of multifactorial phenomena. The various mechanisms of interactions of endogenous and environmental factors with the immune system leading to autoimmune diseases are reviewed in this monograph. In addition to genetic factors, exogenous factors include infections, components in food, drugs and environmental chemicals.

4. Of the environmental factors, drug-induced autoimmune disorders and hypersensitivity reactions are a major concern, and often the reason for withdrawing drugs from the market or restricting their use.

5. In contrast to the great variety of methods for monitoring potential chemical-mediated effects in humans, tests available for measuring responses of the immune system to chemicals that may cause autoimmunity are only poorly validated for clinical purposes.

6. The number of animal models of autoimmunity is extensive. These models represent a variety of systemic and organ-specific diseases, and are mostly used to explore etiology and therapeutic possibilities for certain autoimmune diseases. However, for the purpose of safety evaluation, a general strategy to identify and predict the autoimmunogenic potential of a wide range of chemicals is lacking.

Recommendations

1. There is an urgent need to determine the cause of increased incidences of autoimmune diseases.

2. It is important to devise standard strategies for the clinical investigation and diagnosis of autoimmune diseases and to apply them internationally to examine causes and incidences of autoimmune disorders.

3. Post-marketing surveillance of medicines should be extended to provide screening and alerting systems for autoimmune disorders associated with the medicines.

4. Public health authorities, health professionals, and government agencies should consider how to estimate the human and economic costs to individuals and society of autoimmune diseases.

5. Strategies to identify the ability of chemicals to induce autoimmunity should be developed. Such strategies may include different tiers, i.e. identification of the ability to stimulate the immune system, followed by examination in suitable animal models that use systemic (mostly oral) exposure routes and clinical outcome.

6. In view of the sensitivity of the developing immune system to immunotoxic injury, more emphasis should be placed on studies involving perinatal exposure to chemicals.

13. TERMINOLOGY

Acquired immunity. A state of protection against pathogen-induced injury, with rapid immune elimination of pathogenic invaders; due to previous immunization or vaccination.

Addison's disease. Adrenocortical hypofunction characterized by hypotension, weight loss, anorexia, and weakness. The most common form is the idiopathic Addison's disease, mediated by autoimmune mechanisms. Autoantibodies specific to the adrenal cortex are specific diagnostic markers of this form. 21-hydroxylase, a cytochrome P450 steroidogenic enzyme, is one of the major targets of adrenal autoantibodies in idiopathic Addison's disease as well as in Addison's disease in context of autoimmune polyglandular syndromes (↳ polyendocrinopathies, autoimmune). Hypofunction or failure of the adrenal gland may also be a manifestation of antiphospholipid syndrome due to thrombosis of the blood vessels of the adrenal glands (↳ antiphospholipid syndrome).

Adhesion molecules. Molecules, belonging mainly to the immunoglobulin or integrin superfamily of molecules (e.g., LFA-1, ICAM-1), expressed on the membrane of various cells of the immune system. Interactions with each other as receptors and corresponding ligands facilitate cooperation (cross-talk) of cells, signal transduction and information transfer between cells.

Adjuvant. A material that enhances immune response to substances in a non-antigen-specific manner.

Allogenic. Term describing genetically different phenotypes in different (non-inbred) individuals of the same species.

Alopecia. Loss of hair, often associated with autoimmune disease (e.g., autoimmune thyroid diseases, pernicious anemia, Addison's disease, type 1 diabetes mellitus, systemic lupus erythematosus). Although a specific autoimmune response could not be found up to now, autoimmunity probably plays a role in a subset of this disease.

Alveolitis. Inflammation of the alveoli of the lung. May be a manifestation of systemic autoimmune diseases.

ANCA-associated vasculitides. Group of autoimmune systemic vasculitides associated with anti-neutrophil cytoplasmic autoantibodies (ANCA): Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome.

Anemia. A reduction in number or mass of circulating red blood cells (RBC) that may cause hypoxia in organs or tissue by the reduction in the oxygen-carrying capacity (reduction in haemoglobin concentration) of blood. Anemia is caused either by decreased production or by increased destruction of RBCs. Immune-mediated forms of anemia caused by decreased production of RBCs are autoimmune myelopathies including aplastic anemia, pure red cell aplasia induced by autoantibodies against erythropoietin, pernicious anemia caused by autoantibody-mediated vitamin B12 deficiency (autoantibodies against gastric intrinsic factor lead to decreased absorption of vitamin B12). Autoantibodies against structures of RBCs are a main cause of acquired decreased production of RBCs (see also: autoimmune haemolytic anemia).

Anergy. Lack of immune responsiveness (usually defined as lack of response to common recall antigens). The failure of B- or T- cells to proliferate in response to defined autoantigens (clonal anergy) is a primary mechanism of self-tolerance.

Animal models of autoimmunity. Used for investigations of factors and mechanisms involved in the induction and progression of pathological autoimmunity and disease development with the aim of improvement of diagnosis, prophylaxis and therapy of human autoimmune diseases. However, most experimentally induced or spontaneously occurring animal models usually differ in some aspects from human autoimmunity. Nevertheless, important insights into the pathogenesis of autoimmune diseases can be obtained using animal models, e.g., by immunization, exposure to viruses or xenobiotics, thymectomy, manipulation of the idiotypic network or genetic engineering (transgenic or knockout animals).

Antibody. An immunoglobulin produced by activated B-cells and plasma cells after exposure to an antigen with specificity for the inducing antigen.

Antibody-dependent cell-mediated cytotoxicity (ADCC). Lysis of various target cells coated with antibody by Fc receptor-bearing killer cells, including large granular lymphocytes (NK cells), neutrophils, eosinophils and mononuclear phagocytes.

Antigen. Any compound recognized by antigen-receptor-bearing lymphocytes. Antigens induce immune responses or tolerance. Antigens inducing immune responses only with the help of T-cells are T-dependent antigens, while those that do not need T-help are T-independent antigens. All immunogens are antigens but not all antigens are necessarily immunogens (see also ⟨ immunogens).

Antigen-presenting cells. Cells expressing MHC gene products with the capacity to process and present antigen. ⟨ Macrophages, ⟨ dendritic cells, ⟨ B-lymphocytes, and Langerhans' cells are termed professional or constitutive antigen-presenting cells. However, other cells (such as endothelial cells) can acquire the ability to present antigen in certain pathological conditions.

Antigen processing and presentation. Protein antigens are processed (cleaved by enzymes) in various compartments of antigen-presenting cells. The immunogenic peptides interact with the binding sites of MHC class II products (exogenous antigens) or with those in MHC class I products (endogenous antigens, including viruses). The processed antigen-MHC complex is recognized by the antigen receptor complex of T-lymphocytes.

Antigenic determinant. A single antigenic site (epitope) usually exposed on the surface of a complex antigen. Epitopes are recognized by antigen-receptors on T- or B-cells (T-cell epitopes or B-cell epitopes).

Antimitochondrial antibodies (AMA). Autoantibodies producing a mitochondrial staining on cryostat sections of various tissues and on tumor cell monolayers. According to the fluorescence pattern different subtypes can be differentiated. AMA of the subtyp 2 (AMA-M2) are directed against antigens of three related 2-oxo acid dehydrogenase complexes (e.g., the E2 subunit of the pyruvate dehydrogenase complex, PDC-E2) localized to the inner mitochondrial membrane. AMA-M2 is a specific marker of ⟨ primary biliary cirrhosis.

Anti-neutrophil cytoplasmic autoantibodies (ANCA). Autoantibodies directed against cytoplasmic antigens of neutrophils and monocytes. ANCA are routinely detected by indirect immunofluorescence with three different patterns: cANCA (granular cytoplasmic), pANCA (perinuclear), and xANCA or aANCA (atypical). They are diagnostic markers for systemic necrotizing vasculitides (e.g., \ Wegener's granulomatosis, \ microscopic polyangiitis) and inflammatory bowel diseases. See also: \ Myeloperoxidase (MPO) and \ Proteinase 3 (PR3).

Antinuclear antibodies (ANA). Nonorgan-specific autoantibodies directed against various nuclear antigens including chromatin antigens (e.g. single- or double-stranded DNA, nucleosomes, histone proteins), centromere antigens (e.g. CENP-B protein), nucleolar antigens (e.g., fibrillarin, PM-Scl proteins, RNA polymerases), splicing proteins (e.g., Sm and U1-RNP proteins) and other conserved nuclear proteins (e.g., Ro/SS-A, La/SS-B, DNA topoisomerase I). ANA are frequently observed in patients with autoimmune systemic rheumatic diseases (also called connective tissue diseases), especially in patients with \ systemic lupus erythematosus (SLE), \ systemic sclerosis (scleroderma), \ mixed connective tissue disease (MCTD) and \ Sjögren's syndrome and in patients with \ autoimmune hepatitis type 1.

Antinuclear factor (ANF). Former term for \ antinuclear antibody.

Antiphospholipid antibodies (aPL). Autoantibodies directed against neutral or negatively charged phospholipids including anti-cardiolipin antibodies (aCl) and Lupus anticoagulant. They are diagnostic markers of the \ antiphospholipid syndrome (APS), although they are found also in patients with other (autoimmune) diseases and infections.

Antiphospholipid syndrome (APS). One of the most common autoimmune disease characterized by thrombosis, recurrent spontaneous abortions and the presence of \ antiphospholipid antibodies. APS may occur as an isolated disease (primary APS) or in combination with another autoimmune disease, especially \ systemic lupus erythematosus (secondary APS).

Apoptosis. Programmed cell death, a physiological process whereby useless and potentially harmful cells are rapidly eliminated without tissue inflammation or damage. Important role in embryogenesis and normal tissue homeostasis, but also involved in the development of malignancy and autoimmunity. The dysfunction of an apoptotic pathway (e.g., defects in certain

pro- and anti-apoptotic molecules), defective clearance of apoptotic cells and abnormalities in the mechanisms of clearance, processing and presentation of autoantigens may play an important role in the development of autoimmune diseases. See also: ⟨ Fas and Fas ligand, ⟨ autoimmune lymphoproliferative syndrome, ⟨ Bcl-2.

Atherosclerosis. A type of arteriosclerosis that is characterized by atheroma formation. A multifactorial process leading to accumulation of lipids within the vessel wall, associated with mononuclear cell infiltration and smooth muscle proliferation. Autoimmune mediated inflammation may play an important role in accelerated atherosclerosis in autoimmune rheumatic diseases.

Autoantibodies. Immunoglobulins (antibodies), that are directed against the organisms' own antigens (⟨ autoantigens). They circulate in the serum but may be also detectable in other body fluids or bound in target tissue structures. Autoantibodies may occur as a part of the natural immunoglobulin repertoire (⟨ natural autoantibodies) or are induced by different mechanisms (non-natural or pathological autoantibodies). A number of non-natural autoantibodies are diagnostic markers of defined autoimmune diseases regardless of their pathogenetic activity. They may be directed against conserved nonorgan-specific autoantigens (e.g., ⟨ anti-nuclear antibodies), organ-specific extracellular autoantigens (e.g., glomerular basement membrane autoantibodies), organ-specific cellular antigens (e.g., ⟨ islet cell antibodies) or cell specific autoantigens of circulating cells (e.g., ⟨ anti-neutrophil cytoplasmic autoantibodies).

Autoantigens. Self antigens of the organism, which may be targets of autoimmune responses by autoreactive B-cells (see: ⟨ autoantibodies) or T-cells, including proteins (e.g., enzymes, structural proteins), glycoproteins (e.g., beta2 glycoprotein I), nucleic acids (e.g., double-stranded DNA), phospholipids (e.g., cardiolipin) and glycosphingolipids (e.g., gangliosides).

Autoimmune diseases. Disorders that are characterized (i) by the production of autoantibodies or immune effector cells that are autoreactive to self peptides and (ii) by pathological changes (e.g., tissue infiltration, damage and/or dysfunction) that resulted from these immune responses against self antigens (autoantigens).

Autoimmune haemolytic anemia (AIHA). Acquired haemolytic anemia (see also: \ anemia) mediated by autoantibodies against antigens on the organism's own red cell membrane. AIHA may be idiopathic, secondary to lymphoproliferative, autoimmune (e.g., \ systemic lupus erythematosus) or chronic inflammatory disorders, postinfectious or drug-induced (see also: \ cold autoantibody type, warm autoantibody type, drug-induced immune haemolytic anemia).

Autoimmune hepatitis (AIH). Chronic autoimmune-mediated hepatic inflammation characterized by antinuclear (ANA), smooth muscle (SMA)/anti-F-actin, liver-kidney microsomal (LKM), and soluble liver antigen (SLA) antibodies. 10-20% of all cases of chronic hepatitis. May be idiopathic (AIH type 1, 2, and 3), part of autoimmune polyendocrine syndrome type 1 (APECED hepatitis) or drug-induced. See also: \ liver-kidney microsomal antibodies (LKM), \ liver specific antigens.

Autoimmune lymphoproliferative syndrome (ALPS). Also known as Canale-Smith syndrome. Characterized by lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias and hypergamma-globulinemia. Associated with defects in Fas-FasL apoptosis signalling pathway due to mutations in the \ Fas gene, the FasL gene, or other genes coding for factors of these pathway.

Autoimmune regulator (AIRE). An important DNA binding protein involved in immune regulation (probably in the establishment and maintenance of tolerance). AIRE is expressed mostly in cells of lymphoid tissues. In the thymus, AIRE is expressed in two types of antigen-presenting cells that are central in the negative selection of self-reactive T-cells. The absence of a functional AIRE protein (caused by mutations in both copies of the AIRE-1 gene) results in the APECED syndrome, also known as autoimmune polyglandular syndrome type 1 (see also: \ polyendocrinopathies, autoimmune).

Autoimmunity. Inappropriate reaction of the immune system against the organisms' own antigens (\ autoantigens) that may be either destructive or non-destructive. Destructive autoimmunity is associated with the development of \ autoimmune diseases.

Bcl-2. Human oncoprotein that plays a role in tissue development and maintenance by preventing apoptosis of specific cell types. Animal models suggest that failure to induce normal

levels of apoptosis due to overexpression of Bcl-2 may contribute to the development of lymphoproliferative disorders and acceleration of autoimmunity. The role in human autoimmunity is not clear until now.

B-lymphocytes (B-cells). Bone-marrow-derived lymphocytes, expressing an antigen-receptor complex composed of membrane-bound immunoglobulin (mIg) and associated molecular chains. B-cell receptors interact with epitopes directly (no MHC restriction). Activated B-lymphocytes produce antibody and are efficient antigen-presenting cells. They are the precursors of plasma cells.

Bullous skin diseases, autoimmune. Characterized by intraepidermal or subepidermal blisters (e.g., pemphigus vulgaris, bullous pemphigoid) and highly specific autoantibodies against components of the desmosome or hemidesmosome (e.g., desmoglein 3, BP180). May be idiopathic or paraneoplastic (caused by various lymphoproliferative malignancies).

Cardiolipin. Main target of antiphospholipid antibodies.

Carrier. An immunogenic macromolecule (usually protein) to which a hapten is attached, allowing the hapten to be immunogenic.

CD. A molecular marker on a cell surface that may be used operationally to define phenotype, origin and activation state of the cell.

CD1-restricted T-cells. Regulatory cells involved in controlling autoreactivity.

CD3. A molecule composed of five polypeptide chains associated with the heterodimer T-cell receptor (TCR), forming the T-cell receptor complex (TCR/ CD3); CD3 transduces the activating signals when antigen binds to the TCR.

CD4. A cell surface antigen belonging to the immunoglobulin superfamily of molecules. Marker of T helper cells. As an adhesion molecule, it interacts with the non-polymorphic part of MHC class II gene product.

$CD4^{pos}$ $CD25^{pos}$ T-cells. Subtype of regulatory $CD4^{pos}$ T-cells with potential role in the regulation of the immune homeostasis. Seems to be important in preventing the development of

autoimmune diseases (depletion leads to the spontaneous development of various autoimmune diseases in genetically susceptible animals; transfer prevents the development of organ-specific autoimmunity).

CD5^{pos} B-lymphocytes. Lymphocytes of type B1-a, which are predominant in fetal lymphoid organs and in neonatal cord blood. In adults these cells range from 2-6% of total mononuclear cells in peripheral blood. They utilize an immunoglobulin variable gene repertoire different from that of CD5^{neg} B-cells and produce \ natural autoantibodies. The expansion of autoreactive B1-a cells has been reported in peripheral blood of patients with autoimmune diseases (e.g., \ rheumatoid arthritis, \ Sjögren's syndrome, \ antiphospholipid syndrome). In rheumatoid arthritis, these cells can account for up to 60% of circulating B-cells and may produce \ rheumatoid factor. The pathological relevance of these observations is unclear, however.

CD8. A cell surface molecule belonging to the immunoglobulin superfamily of molecules. Marker of suppressor and cytotoxic T-cells. As an adhesion molecule, it interacts with the MHC class I gene product.

CD8^{pos} T-suppressor cells. Regulatory T-cells that inhibit the proliferation of antigen-specific T-cells. Three different subpopulations have been functionally identified in humans. Functional alterations were shown to be associated with the relapse of autoimmune diseases.

CD16. Low-affinity Fcγ receptor (FcγRIII) expressed mainly on NK-cells, granulocytes and macrophages, mediating ADCC.

CD23. Low-affinity Fcε receptor induced by IL-4 and expressed on activated B-cells and macrophages.

CD25. Alpha-chain of the interleukin 2 receptor expressed mainly on CD4^{pos} T-cells.

CD40 ligand (CD40L): Essential molecule for normal switching signalling through binding to CD40 on B-cells. The interaction of CD40L and CD40 is also critical for optimal T cell function. See also: \ hyper IgM syndrome.

Celiac disease. Also known as gluten sensitive enteropathy (GSE). A lifelong intolerance to a protein fraction of grain (e.g., gluten of wheat) leading to intestinal villous atrophy and crypt hyperplasia and characterized by specific autoimmune responses against tissue transglutaminase.

Cell-mediated or cellular response. A specific immune response in which T-lymphocytes mediate the effects, either through the release of cytokines or through cytotoxicity.

Chemokines. Large family of small secreted proteins (8-15 kDa) that control the trafficking of leukocyte subpopulations, induce leukocyte activation and control lymphocyte differentiation and effector function. May play an important role in the pathogenesis of autoimmune diseases, because the migration and accumulation of leukocytes in the target organs are a critical step for this.

Class I MHC gene products. Antigens encoded by the MHC class I genes are expressed on all nucleated cells. They present antigen-derived peptides of endogenous origin.

Class II MHC gene products. Antigens encoded by the MHC class II genes are expressed on antigen-presenting cells. They present antigen-derived peptides of endogenous origin.

Clonal anergy. State of specific functional unresponsiveness. Failure of B- or T-cells to proliferate in response to antigen by downregulation of the antigen receptor complex and/or cytokine receptors and costimulatory molecules. Primary mechanism involved in the induction and maintenance of self-tolerance.

Clonal deletion. Elimination (e.g., by apoptosis, receptor editing) of self-reacting B- or T-cells during their maturation in central or peripheral lymphoid tissues. Primary mechanism involved in the induction and maintenance of self-tolerance.

Clonal indifference (ignorance). Failure of B- or T-cells expressing anti-self receptors to interact with antigen (e.g., by low valency, low concentration or sequestration of antigens; low receptor avidity; lack of costimulatory molecules). Primary mechanism involved in the induction and maintenance of self-tolerance.

Cold autoantibody type. Autoantibodies that react optimally at low temperatures (0^0-5^0C) with surface antigens of red blood cells. They mediate autoimmune haemolytic anemia either by **cold agglutinins** (cold haemagglutinin disease) or **cold haemolysins** (paroxysmal cold haemoglobinuria).

Complement system. A group of serum proteins with the capacity to interact with each other when activated. The chain reaction of the activated complement components results in formation of a lytic complex and several biologically active peptides of low relative molecular mass (anaphylatoxins). The system can be activated by antigen-antibody complexes (classical pathway) and by other components, e.g., bacteria (alternative pathway). As an effector mechanism of the humoral immune response, the activated complement system facilitates opsonization, phagocytosis and lysis of cellular antigens. Some defects in components of complement are associated with autoimmune diseases (see ⟨ complement deficiency).

Complement deficiency. Congenital deficiencies in the various components of the complement system. Rheumatic disorders (mainly ⟨ systemic lupus erythematosus) are associated with deficiencies of the early components of the classical pathway. More than 30% of individuals with C2 deficiency and nearly 80% with either C3 or C4 deficiency have an autoimmune manifestation.

Connective tissue diseases. Systemic autoimmune rheumatic diseases including ⟨ systemic lupus erythematosus (SLE), ⟨ Sjögren's syndrome, ⟨ systemic sclerosis (scleroderma), autoimmune ⟨ myositis (polymyositis, dermatomyositis), ⟨ mixed connective tissue disease (MCTD) and other overlap syndromes.

Cross-reactivity. The ability of an antibody or a T-cell, specific for one antigen, to react with a second antigen; a measure of relatedness between two antigenic substances, and/or polyspecificity of the antibody molecule (e.g., some rheumatoid factors), or of the T-cell receptor.

Cryoglobulinemic vasculitis. Cutaneous or systemic vasculitis caused by frigolabile proteins (⟨ cryoglobulins, cryofibrinogen) that leads to increased viscosity, protein precipitation or gelatinification, complement activation and endothelial cell damage, especially in the cold.

Frequently associated with chronic hepatitis C or B infection, but can also be induced by other infections and malignancies.

Cryoglobulins. Precipitating immunoglobulins**,** forming insoluble aggregates at temperatures below 25^0C. Many cryoglobulins function as autoantibodies (e.g., rheumatoid factor). Cryoglobulins are found in lymphoproliferative diseases, a number of autoimmune diseases as well as chronic infections. They can lead to vasculitic and secondary thrombotic manifestations (↓ cryoglobulinemic vasculitis, glomerulonephritis).

Cytokines. Group of substances (biologically active peptides), mainly synthesized by lymphocytes (**lymphokines**) or monocytes/ macrophages (**monokines**), that modulate the function of cells in immunological reactions; cytokines include ↓ interleukins. Some cytokines (pleotrophic cytokines) have a broad spectrum of biological actions, including: neuromodulation, growth factor activity and proinflammatory activity.

Cytotoxic T-lymphocyte (CTL). A subpopulation of T-cells with the capacity to lyse target cells displaying a determinant in association with MHC gene products, recognized by its antigen receptor complex (TCR/CD3).

Dendritic cell (DC). A cell type characterized by extended cytoplasmic protrusions and a high expression of adhesion molecules and Class II MHC gene products effecting antigen presentation to specific lymphocytes (see also ↓ Langerhans' cell). DCs also play a crucial role in the establishment of both central and peripheral ↓ self-tolerance.

Dermatitis. Inflammatory skin disease showing redness, swelling, infiltration, scaling and sometimes vesicles and blisters.

Desensitization. Generally transient state of specific non-reactivity in previously sensitized individual, resulting from repeated antigen exposures.

Diabetes mellitus, insulin-dependent (IDDM). Former term for type 1 diabetes mellitus.

Diabetes mellitus, type 1 (T1D). Autoimmune form of diabetes mellitus caused by immune-mediated destruction of insulin-producing beta-cells in the pancreas with irreversible loss of insulin production. \ islet cell autoantibodies (ICA) and autoantibodies directed against \ glutamic acid decarboxylase (GAD), insulin and the IA2-antigen are diagnostic markers for T1D as well as risk markers of the development of this disease.

Double-stranded DNA (dsDNA). Main target of autoantibodies in patients with \ systemic lupus erythematosus. **DsDNA autoantibody** is a diagnostic marker and classification criterium of this disease.

D-penicillamine. A drug that is able to induce a variety of autoantibodies and autoimmune diseases (e.g., \ myasthenia gravis, polymyositis). Disease usually remits within 1 year after the medication is stopped.

Drug-induced lupus (DIL). A lupus-like disorder induced by various medications that is mainly characterized by the occurrence of arthralgia, myalgia, pleuritis, erythema, fever and anti-nuclear antibody (ANA) production. The clinical symptoms disappear within a few days to weeks after withdrawal of the causative drug, and the associated autoimmune phenomena disappear within the course of a year. **Classical DIL-inducing drugs** are procainamide, hydralazine and quinidine.

Drug-induced immune haemolytic anemia. Anemia caused by drug-mediated immune haemolysis of red blood cells (RBC) through different antibody-mediated mechanisms: (i) drug adsorption mechanism (antibody directed against the drug bound to RBC surface antigen), (ii) ternary (immune) complex mechanism (antibody form a trimolecular complex with the drug and RBC membrane antigen) and (iii) true autoantibody-mediated mechanism (drug-induced antibodies bind RBCs in the absence of the drug).

Eczema. A dermatitis characterized by non-contagious inflammation of skin with typical clinical (itch, erythema, papules, seropapules, vesicles, squames, crusts, lichenification) and dermatohistological (spongiosis, acanthosis, parakeratosis, lymphocytic infiltration) findings. Often due to sensitization.

Endocytosis. The uptake by a cell of a substance from the environment by invagination of its plasma membrane; it includes both phagocytosis mediated by receptors and pinocytosis.

Enzyme-linked immunosorbent assay (ELISA). An assay in which an enzyme is linked to an antibody and a labelled substance is used to measure the activity of bound enzyme and, hence, the amount of bound antibody. With a fixed amount of immobilized antigen, the amount of labelled antibody bound decreases as the concentration of unlabelled antigen is increased, allowing quantification of unlabelled antigen (**competitive ELISA**). With a fixed amount of one immobilized antibody, the binding of a second, labelled antibody increases as the concentration of antigen increases, allowing quantification of antigen (**sandwich ELISA**). ELISAs are used for the specific determination of ⟨ autoantibodies.

Epidemiology. The study of the distribution and determinants of health-related states or events in specified populations, and the application of this knowledge to manage health problems.

Epitope. Antigenic determinant, a structure of biological molecules that mediate specific recognition by the immune system.

Epitope spreading. Increase in the number of epitopes targeted by autoantibodies and/or T-cells. May be on the same autoantigen (intramolecular epitope spreading) and/or on other autoantigens (intermolecular epitope spreading). Characteristic sign of progression of autoimmune disease from initial activation to a chronic state.

Exogen-autoimmune encephalomyelitis (EAE). Autoimmune demyelinating disease induced in genetically susceptible mice, rats or marmosets by immunization with myelin proteins or peptides. Animal model for ⟨ multiple sclerosis.

Exogen-allergic encephalomyelitis: former term for ⟨ exogen-autoimmune encephalomyelitis (EAE).

Experimental autoimmune thyroiditis (EAT). Autoimmune thyroiditis experimentally induced in several strains of mice and rats by immunization with thyroglobulin or by neonatal thymectomy.

Fas. Differentiation antigen (synonyms: APO-1, CD95) expressed on a variety of cell lines including myeloid and lymphoblastoid cell lines. The primary role is to regulate peripheral immune responses, which is achieved by triggering \ apoptosis. Mutations of Fas or its ligand (FasL) are associated with peripheral lymphoid tissue expansion and autoimmune diseases. See also \ autoimmune lymphoproliferative syndrome.

Fc receptors. Receptors expressed on a wide range of cells, interacting with the Fc portion of immunoglobulins belonging to various isotypes. Membrane-bound Fc receptors mediate different effector functions (endocytosis, antibody-dependenT-cellular cytotoxicity (ADCC)) and induce mediator release. Both the membrane-bound and soluble forms of Fc receptors regulate antibody production of B-cells.

FOXP3. Transcription repressor that is specifically expressed in $CD4^{pos}CD25^{pos}$ T-cells. Mutations in the FOXP3 gene may lead to an autoimmune syndrome called \ IPEX (immunodysregulation-polyendocrinopathy-enteropathy-x-linked).

Gangliosides. Components of all vertebrate cell membranes. Glycolipids which are expressed at high densities in peripheral nervous tissues. Targets of autoantibodies in autoimmune \ peripheral neuropathies (e.g., anti-GM1, -GQ1b, -GD1b). Induced by infection, \ natural autoantibodies crossreacting with gangliosides may become pathogenic after affinity maturation and class switching.

Gastritis, autoimmune. Autoimmune mediated destruction of the gastric mucosa that may result in the development of \ pernicious anemia. Autoimmune gastritis is associated with autoantibodies to H^+/K^+ ATPase of gastric parietal cells as well as autoantibodies to the intrinsic factor produced by these cells.

Gliadin. A protein that is found in wheat and some other grains, including oats, rye, barley, and millet. People with \ celiac disease are sensitive to gliadin in the diet and produce antibodies to gliadin as well as autoantibodies to \ tissue transglutaminase.

Glomerular basement membrane (GBM). Target of autoantibodies in patients with Goodpasture's disease. The autoantigenic epitope is a peptide on the α3 chain of type IV collagen which is also found in renal tubular and alveolar basement membrane.

Glomerulonephropathy. Disease of the glomeruli, which may show either thickening of the basement membrane membranous glomerulopathy associated with IgG deposits due to the accretion of proteins, or a minimal change glomerulopathy, in which there is functional damage but little structural change by light microscopy.

Glutamic acid decarboxylase (GAD). Main autoantigen in diabetes mellitus type 1 and Stiff-Person-Syndrome (a neurologic autoimmune disease). Localized in pancreatic beta-cells and GABAergic neurons.

Goodpasture's disease/syndrome. An autoimmune pulmonary-renal syndrome characterized by pulmonary hemorrhage, glomerulonephritis, and production of autoantibody to glomerular basement membrane (GBM); Anti-GBM disease.

Graves' disease. Hyperthyroidism associated with diffuse hyperplastic goiter resulting from production of a thyroid-stimulating hormone receptor (TSH-R) binding autoantibody.

Hapten. A non-immunogenic compound of low relative molecular mass which becomes immunogenic after conjugation with a carrier protein or cell and in this form induces immune responses. Antibodies, but not T-cells, can bind the hapten alone in the absence of carrier.

Hashimoto's thyroiditis. Goitrous form of diffuse autoimmune thyroiditis. See also: thyroiditis, autoimmune.

Helper T-lymphocyte. A functional subpopulation of T-cells (expressing CD4 antigen) that help to generate cytotoxic T-cells and cooperate with B-cells in the production of an antibody response. Helper T-cells recognize antigen in association with MHC class II gene products. Depending on their capacity to produce various cytokines one can functionally differentiate Th1 (IL-2 and IFN gamma producing) and Th2 (IL-3, IL-4 and IL-6 producing) cells.

Heparin-induced thrombocytopenia (HIT). Most frequent antibody-mediated drug-induced thrombocytopenia. Occurs in 1-2% of patients treated with heparin i.v. longer than four days. Mediated by antibodies to complexes formed between heparin and the endogeneous platelet factor 4 (PF4).

Hepatitis, chronic. see: ⟨ autoimmune hepatitis.

Human leukocyte antigen (HLA). The major human histocompatibility complex situated on chromosome 6. Human HLA-A, -B and -C (resembling mouse H-2K, D and L) are class I MHC molecules, whereas HLA DP, -DQ and -DR (resembling mouse I-A and I-E) are class II MHC molecules.

Humoral immune response. An immune response in which specific antibodies induce the effector functions (such as phagocytosis and activation of the complement system).

Hypergammaglobulinemia. Increase of gammaglobulins in the blood by paraproteinemia or increased production of ⟨ immunoglobulins.

Hyper IgM syndrome (HIGM): Primary T cell defect due to mutations in the CD40 ligand. Characterized by recurrent (opportunistic) infections and very low levels of IgG and IgA. Autoimmune manifestations (e.g., cytopenia, arthritis, sclerosing cholangitis) are often seen.

Hyperreactivity. An abnormally increased response to a stimulus.

Hypersensitivity. Abnormally increased immunologically mediated response to a stimulus. Sometimes used loosely for any increased response.

Hypersusceptibility. Adverse effects in an individual occurring under exposure conditions that result in no effects in the great majority of the population or an individual exhibiting exaggerated effects in comparison with the great majority of those showing some adverse effects.

Hyperthyroidism. Hyperactivity of the thyroid gland. Autoimmunity is the commonest cause of hyperthyroidism, accounting for 60-80% of cases. See also: ⟨ Graves' disease.

Hypothyroidism. Hypofunction (insufficiency) of the thyroid gland. Autoimmunity is the commonest cause of hypothyroidism in iodine-sufficient countries. See also: \ thyroiditis, autoimmune; Hashimoto's disease; primary myxedema.

Idiopathic thrombocytopenic purpura (ITP). Autoantibody-mediated thrombocytopenia (autoimmune thrombocytopenic purpura).

Idiopathic. A term that describes a "primary" symptom or disease, in which no underlying cause or associated disorder could be found. In most cases autoimmune processes are involved in the pathogenesis (e.g., idiopathic thrombocytopenic purpura, idiopathic Addison's disease).

Idiosyncrasy. An unusual individual reaction to food or a drug not related to allergy or \ autoimmunity.

Idiotype. Unique, genetically controlled determinants present on \ immunoglobulin variable domains and determine the antibody specificity.

Idiotypic network. Feedback inhibition of ongoing B- or T-cell responses by a network of (anti-idiotype--idiotype) interactions. Secondary mechanism involved in the induction and maintenance of \ self-tolerance.

Immune complexes (IC). Antigen-antibody complexes formed every time antibody meets antigen. May become pathogenic by triggering a variety of inflammatory processes if not removed effectively from circulation or if formed in situ. IC play a role in vasculitic manifestations of autoimmune diseases (e.g., lupus nephritis).

Immune deviation. A regulatory mechanism of the preferential activation of one arm (cellular vs. humoral; see also \ Th1- and \ Th2-cells) of the adaptive immune system at the expense of the other. Although not a form of true tolerance this regulatory mechanism may be involved in the induction and maintenance of \ self-tolerance.

Immunodeficiency. Defects in one or more components of the immune system resulting in inability to eliminate or neutralize non-self antigens. Congenital or primary immunodeficiencies

are genetic or due to developmental disorders (such as congenital thymic aplasia). Acquired or secondary immunodeficiencies develop as a consequence of malnutrition, malignancies, immunosuppressive compounds, radiation or infection of immunocompetent T-cells with human immunodeficiency virus (HIV). Defects of the nonspecific defence system may also result in immunodeficiency. Immunodeficiency and autoimmune phenomena may occur concomitantly in the same individual. Many immunodeficiency syndromes are associated with autoimmune diseases (see also: ⟍ complement and ⟍ selective IgA deficiency, ⟍ hyper IgM syndrome). Immune dysregulation, persistent antigen stimulation, recurrent tissue damage and defective clearance of immune complexes are pathogenic factors that may lead to autoimmunity in immunodeficient individuals.

Immunogen. A substance capable of eliciting a specific immune response manifested by the formation of specific antibodies and/or specifically committed lymphocytes. To induce an antibody response an immunogen must possess structurally and functionally distinct determinants for activation of B-cells and T-cells.

Immunoglobulin (Ig). Immunity-conferring portion of the plasma- or serum-gammaglobulins. Various isotypes (classes and subclasses) of immunoglobulins have a common core structure of two identical light (L) and two identical heavy (H) polypeptide chains, which contain repeating homologous units folded in common globular motifs (Ig domains). The amino acid sequences of the N-terminal domains are variable (V domains), in contrast to the more conserved constant regions (C domains). The V domains contain the complementarity-determining regions (CDRS) forming the antigen-binding sites, whereas the C domains trigger several effector functions of the immune system (see also ⟍ antibody).

Immunoglobulin gene superfamily. Genes encoding proteins containing one or more Ig domains (homology units) that are homologous to either Ig V or C domains. Cell surface and soluble molecules mediating recognition, adhesion or binding functions in and outside the immune system, derived from the same precursor, belong to this family of molecules (e.g., Ig, TCR, MHC Class I and II, CD4, CD8, FcγR, NCAM, PDGFR).

Incidence (epidemiological). The number of new cases of disease in a defined population during a specified period of time.

Indirect immunofluorescence. Screening method for the presence of non-organ and organ specific autoantibodies. Tumor cell monolayer (e.g., Hep-2 cells for analysing ↓ antinuclear antibodies), cytocentrifuged cells (e.g., neutrophile granulocytes for analysing ↓ anti-neutrophil cytoplasmic autoantibodies) or organ cryostat section (e.g., liver and kidney for analysing ↓ liver-kidney microsomal antibodies, pancreas for analysing ↓ islet cell antibodies) are used as targets.

Infertility, autoimmune. Caused by sperm antibodies, autoimmune ovarian inflammation (oophoritis) or autoimmune orchitis. May be part of ↓ polyendocrinopathies.

Inflammatory bowel diseases. Chronic, relapsing and tissue-destructive idiopathic intestinal inflammation probably as a result of inappropriate responses to luminal antigens (e.g., food breakdown products, bacterial products, or ↓ autoantigens). Autoantibodies against proteins of neutrophile granulocytes, pancreatic acinus, intestinal goblet and colonic epithelial cells are detectable. Subtypes that differ in clinic, histology and serology are Crohn's disease (CD) and ulcerative colitis (UC). CD is immunologically characterized by antibody to mannan of *Saccharomyces cerevisiae* and ↓ Th1-cell dominated responses.

Interclonal competition. Favouring of foreign-specific lymphocytes at the expense of self-specific lymphocytes. Secondary mechanism involved in the induction and maintenance of ↓ self-tolerance.

Interleukin. Immunoregulatory proteins, also designated as lymphokines, monokines or cytokines. General features are: low relative molecular mass (<80 000) and frequently glycosylated; regulate immune cell function and inflammation by binding to specific cell surface receptors; transient and local production; act in paracrine, autocrine or endocrine manner, with stimulatory or blocking effect on growth/differentiation; very potent, function at picomolar concentrations. Interleukins represent an extensive series of mediators with a wide range of overlapping functions. Other mediators in this series are *c*-kit ligand, interferons, tumour necrosis factor, transforming growth factor, and a family of low relative molecular mass mediators, called ↓ chemokines.

Intolerance. Non-immunologically mediated adverse reactions. In food intolerances these may be due to pharmacological properties of food constituents, metabolic disorders or responses of unknown etiology.

IPEX. X-linked syndrome characterized by immunodysregulation, polyendocrinopathy (type 1 diabetes, thyroidites), hemolytic anemia, thrombocytopenia, dermatitis and enteropathy, caused by mutations in ⟨ FOXP3.

Iron. Vital metal for the proliferation of all cells including those of the immune system. May be involved in the induction of autoimmunity by influencing the antigen presentation (catalysing the production of cryptic epitopes of autoantigens).

Islet cell antibodies (ICA). Autoantibodies reacting with endocrine (pancreatic islet) cells and detectable by indirect immunofluorescence on pancreas kryostat sections. Diagnostic marker of ⟨ diabetes mellitus type 1.

Kidney diseases, autoimmune. May be due to immunologic reaction to renal antigens (⟨ glomerular basal membrane, ⟨ Goodpasture's syndrome) or part of systemic autoimmune disease (e.g., ⟨ systemic lupus erythematosus, ⟨ ANCA-associated vasculitides).

Langerhans' cells. Bone-marrow-derived epidermal cells with a dendritic morphology, expressing CD1 marker in humans and containing the cytoplasmic organelle, called the Birbeck granule. They express Class II MHC antigen and are capable of antigen presentation (see also ⟨ dendritic cells).

Lambert-Eaton myasthenic syndrome (LEMS). Paraneoplastic neurological disorder associated with small cell lung cancer and caused by autoantibodies against voltage-gated calcium channels.

Leukocytopenia. Amount of leukocytes below normal values. Characteristic feature of systemic autoimmune diseases (e.g., Felty's syndrome, ⟨ systemic lupus erythematosus, ⟨ Sjögren's syndrome, ⟨ mixed connective tissue disease).

Leukocytosis. Abnormal increase in the number of white blood cells.

Liver disease, autoimmune. Diseases caused by autoimmune-mediated inflammation and/or fibrosis: ⟨ autoimmune hepatitis, ⟨ primary biliary cirrhosis, and primary sclerosing cholangitis.

Liver-kidney microsomal antibodies (LKM). Autoantibodies directed against cytochrome P450 and UDP-glucuronosyltransferase (UGT) antigens typically found in patients with immune-mediated hepatitis: **LKM-1** antibodies (cytochrome P450 2D6) in patients with autoimmune hepatitis type 2 (AIH-2) and autoimmunity associated with hepatitis C; **LKM-2** (cytochrome P450 2C9) in patients with drug-induced hepatitis caused by tienilic acid; **LKM-3** (UGT-1) in patients with chronic hepatitis D and AIH-2.

Liver specific antigens. Some of these become targets of autoantibodies. Liver microsomal (**LM**) antibodies reacting with cytochrome P450 1A2 are found in patients with drug-induced hepatitis due to dihydralazine or in autoimmune hepatitis (AIH) as part of autoimmune polyendocrine syndrome type 1. Autoantibodies against soluble liver (**SLA**) or liver-pancreas (**LP**) antigen are found in AIH patients. Autoantibodies against asialoglycoprotein receptor (**ASGPR**) are frequently found in autoimmune liver diseases, but also in viral-induced and other liver inflammation.

Long-acting thyroid stimulator (LATS). Former term for TSH-R stimulating autoantibodies. See also: ⟨ thyroid-stimulating hormone receptor (TSH-R).

Lymphocytopenia. Amount of lymphocytes below normal values. Characteristic feature of systemic autoimmune diseases (e.g., ⟨ systemic lupus erythematosus, ⟨ Sjögren's syndrome, ⟨ mixed connective tissue disease).

Lymphocyte. Bone-marrow-derived cell with little cytoplasm, with the ability to migrate and exchange between the circulation and tissues, to home to sites of antigen exposure, and to be held back at these sites. The only cells that specifically recognize and respond to antigens (mainly with the help of accessory cells). Lymphocytes consist of various subsets differing in their function and products (e.g., ⟨ B-lymphocytes, ⟨ helper-T-lymphocytes, ⟨ cytotoxic T--lymphocytes, ⟨ regulatory T-cells).

Macrophage. Mononuclear cells derived from monocytes residing in tissues. Activated by different stimuli they may appear in various forms such as epitheloid cells and multinucleate giant cells. Macrophages found in different organs and connective tissues have been named according the specific locations, e.g., as microglia, alveolar macrophages or Kupffer cells. Macrophages may function as antigen-presenting cells, effector cells of cell-mediated immunity, and phagocytes eliminating opsonized antigens.

Major histocompatibility complex (MHC). A cluster of genes encoding cell surface antigens that are polymorphic within a species and have a crucial function in signalling between lymphocytes and cells expressing antigen and in recognition of self.

Microchimerism. A state, in which a small number of cells or DNA from one individual harbored in another individual. Fetal as well as maternal microchimerism may be involved in the pathogenesis of autoimmune disease (e.g., systemic sclerosis).

Microscopic polyangiitis (MPA). ANCA-associated necrotizing, pauci immune vasculitis of the small vessels (capillaries, venules, arterioles) frequently associated with rapidly progressive glomerulonephritis and/or hemorrhagic alveolitis as well as autoantibodies against myoleoperoxidase.

Mitogen. A substance that causes cells to synthesize DNA and proliferate without acting as an antigen.

Mixed connective tissue disease (MCTD). Systemic autoimmune disease with features of systemic lupus erythematosus, systemic sclerosis, and dermatomyositis/polymyositis and high titered autoantibodies against U1-RNP specific proteins.

Molecular mimicry. Existence of a cross-reactive epitope between microbial proteins and autoantigens. Suggested as one cause of initiating pathologic autoimmunity.

Monocyte. Bone-marrow-derived mononuclear phagocytic leukocyte, with bean-shaped nucleus and fine granular cytoplasm containing lysosomes, phagocytic vacuoles and cytoskeletal filaments. Once transported to tissues they develop into macrophages.

Multiple sclerosis. Autoimmune disorder characterized by destruction of myelin in the central nervous system.

Muscle diseases, autoimmune. Autoimmune diseases associated with profound weakness due to immunological injury of the myofiber (↓ myositis) or affecting the neuromuscular junction (↓ myasthenia gravis, ↓ Lambert-Eaton myasthenic syndrome).

Myasthenia gravis, acquired. The most well understood autoimmune disease. Muscle weakness usually affecting ocular and oropharyngeal muscles due to an autoimmune attack against the neuromuscular junction (e.g., nicotinic acetylcholine receptor). May be idiopathic, paraneoplastic (thymic tumor) or drug-induced (D-penicillamine).

Myeloperoxidase (MPO). This enzyme of azurophilic granules of neutrophils is the major target of pANCA (see: ↓ anti-neutrophil cytoplasmic autoantibodies). **MPO autoantibodies** are diagnostic markers for ↓ microscopic polyangiitis, rapidly progressive glomerulonephritis and ↓ Goodpasture's syndrome. They are also found in patients exposured to silica or drugs (e.g., hydralazine, propylthiouracil, D-penicillamine) as well as in patient with connective tissue and other autoimmune diseases.

Myositis, autoimmune. Rare systemic inflammatory myopathies including primary polymyositis, primary dermatomyositis, myositis associated with malignancy, childhood dermatomyositis and myositis with multisystem autoimmune disease (e.g., mixed connective tissue disease, systemic sclerosis). Autoantibodies against aminoacyl-tRNA synthetases (e.g., anti-Jo-1), signal recognition particle (e.g., anti-SRP54), nuclear helicase (anti-Mi-2), tRNA and tRNA-protein complexes (e.g., anti-Mas) and translation factor (anti-KJ) have been described as myositis specific.

Natural autoantibodies (NAA). Part of the natural occurring repertoire of polyreactive antibodies that bind to self antigens with low affinity. They are mainly of IgM isotyp and produced by ↓ $CD5^{pos}$ B-lymphocytes. Natural antibodies and its producing cells may have a physiological role in the following processes: (1) first line of protection against external invaders, (2) elimination of degraded autoantigens and senescent cells, and (3) tolerization of T-

cells by presenting self antigens, thereby in protecting from development of pathologic autoimmunity. On the other hand, NAA may become pathogenic in clonal B-cell disorders, e.g., monoclonal anti-I antibodies in cold agglutinin disease cause \ autoimmune haemolytic anemia.

Natural killer (NK) cell. A subset of lymphocytes found in blood and some lymphoid tissues, derived from the bone marrow and appearing as large granular lymphocytes (LGL). NK-cells possess the capacity to kill certain tumour cells or virus-infected normal cells. The killing is not induced by specific antigen and is not restricted by MHC molecules.

Nephritis, autoimmune. Inflammation of the kidney (proteinuria and nephritic urinary sediment) due to immunologic reaction to renal antigens (anti-GBM disease, \ Goodpasture's disease; autoimmune tubulointerstitial nephritis with antibody to tubular basement membrane) or as part of systemic autoimmune diseases independent of renal autoantigens (lupus nephritis in \ systemic lupus erythematosus, interstitial nephritis in \ Sjögren's syndrome, nephritis in \ ANCA-associated vasculitis, cryoglobulinemic vasculitis or hypocomplementemic urticarial vasculitis syndrome).

Nephropathy. Disease of the kidney that may involve either or both the glomeruli (specialized structures where blood is filtered) and the renal tubules (connected structures where the composition of the filtrate is greatly modified in accordance with the physiological needs of the body).

Nephrotic syndrome. A clinical disease in which damage to glomeruli has caused leaky filtration, resulting in major loss of protein from the body

Neuropathies, autoimmune. Autoimmune diseases of the nervous system are a major concern in neurologic practice. More and more neuropathies are described as autoimmune or possible autoimmune in nature. Little is known about xenobiotics in the pathogenesis, but infections may play an important role in the initiation of some diseases. Autoimmune neuropathies may be manifested at the neuromuscular junction (see also: \ muscle diseases, autoimmune), as central nervous system diseases (e.g., multiple sclerosis, paraneoplastic neurologic syndromes, stiff-person-syndrome, as well as manifestations of systemic autoimmune diseases) and diseases of the peripheral nerves (e.g., various forms of acute and chronic demyelinating neuropathies).

Neutrophil (polymorphonuclear leukocyte). Granular leukocytes having a nucleus with three to five lobes and fine cytoplasmic granules stainable by neutral dyes. The cells have properties of chemotaxis, adherence to immune complexes, and phagocytosis. The cells are involved in a variety of inflammatory processes including late-phase allergic reactions.

Natural resistance-associated macrophage protein (NRAMP1). Iron transporter that plays a critical role in macrophage activation and differentiation. Allele 3 of the NRAMP1 promoter is associated with autoimmune disorders (e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes mellitus, multiple sclerosis).

Oncogenes. Genes which can potentially induce neoplastic transformation. See also ⟨ Proto-Oncogenes.

Opsonization. Coating of antigens with antibody and/or complement components. The interaction of opsonized complexes with Fc- or complement-receptors facilitates their uptake by the receptor-bearing phagocytic cells.

Oral tolerance. Orally induced and immune-mediated non-responsiveness.

Ouchterlony technique. Double-radial immunodiffusion for the detection of precipitating autoantibodies against “extractable nuclear antigens”. Method of high diagnostic specificity but low sensitivity for diagnosis of autoimmune rheumatic diseases.

Paraneoplastic autoimmune syndromes. Autoimmune diseases that are caused by tumor induced perturbations of the immune system with damaging effects on various organ systems (e.g. cancer-associated retinopathy, ⟨ paraneoplastic neurologic syndromes, paraneoplastic cutaneous syndromes). In most cases, autoantibodies generated by antitumor immunity are responsible for the tissue injury.

Paraneoplastic neurologic syndromes. Group of neurologic disorders mainly caused by cancer-induced immune mechanisms. Any part of the nervous system may be affected. In most cases, the neurologic symptoms (e.g., different forms of encephalitis, cerebellar degeneration, stiff-person syndrome, sensory neuronopathy, myasthenic syndromes, peripheral neuropathies) precede the diagnosis of cancer. Autoantibodies against neuromuscular junction (e.g., against proteins of acetylcholine receptor, calcium and potassium channels), Purkinje cells (e.g. anti-Yo)

and anti-neuronuclear antibodies (ANNA, e.g., anti-Hu, anti-Ri) are highly specific for these syndromes.

Peripheral neuropathies, autoimmune. Acute or chronic inflammatory neuropathies leading to demyelination and axonal damage of nerves and nerve roots associated with high-titred autoantibodies against ↓ gangliosides (e.g., Guillain-Barré syndrome, Miller-Fisher syndrome, acute sensory ataxic neuropathy).

Pernicious anemia. End stage of 10-15% of ↓ autoimmune gastritis due to vitamin B12 malabsorption caused by depletion of gastric parietal cells and autoantibodies against intrinsic factor. Associated with a variety of autoimmune endocrine diseases (e.g., ↓ Hashimoto's thyroiditis, ↓ Addison's disease) and autoimmune myasthenic syndromes.

Photosensitivity. Skin reddening due to an abnormal reaction to sunlight. A characteristic symptom of systemic autoimmune diseases (e.g., ↓ systemic lupus erythematosus, ↓ mixed connective tissue disease), cutaneous and ↓ subacute cutaneous lupus erythematosus.

Plasma cell. A terminally differentiated B-lymphocyte with little or no capacity for mitotic division, that can synthesize and secrete antibody. Plasma cells have eccentric nuclei, abundant cytoplasm and distinct perinuclear haloes. The cytoplasm contains dense rough endoplasmic reticulum and a large Golgi complex.

Polyendocrinopathies, autoimmune. Autoimmune diseases affecting multiple endocrine organs: (i) The autoimmune polyglandular syndrome type 1 (**APS-1**) is characterized by mucocutaneous candidiasis in association with endocrine manifestation (also called **APECED syndrome**: autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy), while (ii) the autoimmune polyglandular syndrome type 2 (**APS-2**) exhibits any combination of adrenal insufficiency (see: ↓ Addison's disease), type 1 diabetes mellitus (see: ↓ diabetes mellitus, insulin-dependent), lymphocytic thyroiditis (see: ↓ thyroiditis, autoimmune), hypoparathyroidism, and gonadal failure. In both types organ-specific autoantibodies against a variety of endocrine glands are detectable. See also: ↓ autoimmune regulator (AIRE).

Prevalence (epidemiology). The number of cases of disease occurring in a given population at a designated time.

Primary biliary cirrhosis (PBC). Autoimmune liver disease that results in the destruction of bile ducts leading to fibrosis and cirrhosis. PBC-specific are \ antimitochondrial antibodies (AMA) directed against proteins of the pyruvate dehydrogenase complex (mainly the E2 subunit).

Primary sclerosing cholangitis (PSC). Chronic, nonbacterial inflammatory narrowing of the bile ducts. Often associated with ulcerative colitis.

Primary myxedema. Atrophic form of diffuse autoimmune thyroiditis (see also thyroiditis, autoimmune).

Prolactin. A versatile hormone that is involved in the regulation of proliferation and differentiation of a variety of cells in the immune system. May play a role in the pathogenesis and clinical expression of autoimmune diseases (e.g., \ systemic lupus erythematosus).

Proteinase 3 (PR3). This multifunctional enzyme of azurophilic granules of neutrophils and monocytes is the major target of cANCA (see: \ anti-neutrophil cytoplasmic autoantibodies). **PR3 autoantibodies** are diagnostic markers for \ Wegener's granulomatosis (WG) and involved in the pathogenesis of this disease. They are also found at low frequencies in patients with other autoimmune systemic vasculitic diseases.

Proteinuria. Main symptom of \ nephritis.

Proto-Oncogenes. Genes that may be involved in neoplastic transformation. The products of proto-oncogenes are important regulators of biological processes (e.g. growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, transcription factors). Mutations or aberrant expression of some proto-oncogenes may be involved in the pathogenesis of autoimmune diseases. See also \ bcl-2.

Rate (epidemiology). The frequency with which an event occurs in a defined population.

Raynaud's phenomenon. Vasospastic condition characterized by acral circulatory disorders affecting the hands and feet. The symptoms can be triggered by cold, dampness or emotional stress. Characteristic feature of systemic autoimmune diseases. Occurs in all or virtually all patients with ⇂ systemic sclerosis, ⇂ mixed connective tissue disease (MCTD) and polymyositis/scleroderma overlap syndrome.

Regulatory T (Treg) cells. Cells that control the maintenance of normal immune homeostasis. They are involved in controlling (anergizing or counter-regulating) autoreactive cells that escaped from thymic negative selection. See also: ⇂ $CD8^{pos}$ T-suppressor cells, ⇂ $CD4^{pos}CD25^{pos}$ cells, ⇂ CD1-restricted T-cells, T-cells with γ/δreceptors).

Rheumatoid arthritis (RA). An episodic inflammatory systemic disease with autoimmune pathogenetic mechanisms. It primarily affects the joints, causing symmetrical lesions and severe damage to the affected joints. RA is the most common form of inflammatory joint disease (prevalence about 0,5-1%).

Rheumatoid factor (RF). Autoantibodies directed against the Fc region of altered IgG immunoglobulin. Although detectable in various diseases, RF is used as a classification criterion of ⇂ rheumatoid arthritis.

Selective IgA deficiency (SIgAD). The most common form of primary immunodeficiency. Autoimmunity is the most prevalent manifestation of this deficiency. Individuals with SIgAD have an increased risk to develop systemic (e.g., ⇂ systemic lupus erythematosus, ⇂ rheumatoid arthritis) and organ-specific (e.g., ⇂ celiac disease) autoimmune disorders.

Self-antigens: see ⇂ autoantigens

Self-tolerance. Specific immunological unresponsiveness to a defined ⇂ autoantigen. Primary (⇂ clonal deletion, ⇂ anergy, ⇂ clonal indifference) and secondary or regulatory (⇂ interclonal competition, ⇂ suppression, ⇂ immune deviation, ⇂ vetoing, feedback regulation by the ⇂ idiotypic network) mechanisms are involved in the induction and maintenance of self-tolerance. Breaking self-tolerance may lead to pathological autoimmunity and development of autoimmune disease.

Sex hormones. Affect the immune system directly (e,g., by modulating the activity of $CD4^{pos}$ cells and cytokine production and in turn by influencing B cell function and by affecting apoptosis of lymphocytes) or indirectly (e.g., by acting on a wide range of target tissues), and may thereby be involved in the development of pathologic autoimmunity.

Sjögren's syndrome. Chronic inflammatory autoimmune disease of the exocrine glands of unknown etiology. Its primary symptoms are keratoconjunctivitis sicca and xerostomia. Two types of Sjögren's syndrome are distinguished: a primary (isolated) type and a secondary type associated with another underlying autoimmune disease (e.g., ⇂ rheumatoid arthritis, ⇂ systemic lupus erythematosus, ⇂ systemic sclerosis, primary biliary cirrhosis, autoimmune hepatitis, multiple sclerosis, autoimmune thyroiditis, etc.). Ro/SS-A and La/SS-B autoantibodies are used as classification criteria.

Spontaneous autoimmune thyroiditis (SAT). Autoimmune thyroiditis that develops spontaneously (without any apparent cause or manipulation) in certain strains of mice and rats (e.g., NOD mice, BB and BUF rats) as well as in other animals (e.g., OS chickens, marmoset monkeys, beagles).

Stem cell. Pluripotent cells, representing 0.01% of bone marrow cells, having the capacity for self renewal, and committed to differentiate along particular lineages, e.g., erythroid, megakaryocytic, granulocytic, monocytic and lymphocytic. Cytokines stimulate the proliferation and maturation of distinct precursors.

Subacute cutaneous lupus erythematosus (SCLE). A chronic remitting form of dermatitis characterized by severe photosensitivity and Ro/SS-A and La/SS-B autoantibodies.

Suppression. Dominant immunological tolerance, a phenomenon which plays an active role in regulating T- and B-cell responses to both foreign and self antigens (⇂ suppressor T-lymphocyte). The downregulation of responses to self antigens is a major regulatory mechanism involved in the induction and maintenance of ⇂ self-tolerance.

Suppressor T-lymphocyte. A subpopulation of T-lymphocytes that inhibits the activation phase of immune responses. They are $CD8^{pos}$, and their growth and differentiation may be regulated by $CD4^{pos}$ cells.

Systemic lupus erythematosus (SLE). A chronic, remitting relapsing inflammatory autoimmune disease affecting multiple organ systems such as the skin, joints, serosal membranes, kidneys, blood cells and CNS. The disease is very heterogeneous in clinical expression and serological factors. Autoantibodies directed against nuclear components (antinuclear antibodies) are typically detected. Anti-dsDNA, anti-Sm and anti-phospholipid antibodies are used as classification criteria.

Systemic sclerosis (SSc). Fibrosing disease of unclear etiology that affects multiple organ systems. The skin ("scleroderma") and blood vessels (arteries, small vessels) are most commonly affected, but involvement of the lungs, gastrointestinal tract (esophagus) may also be observed. Anticentromer antibodies (ACA) as well as autoantibodies against DNA topoisomerase I (scl-70) and various nucleolar antigens are diagnostic and prognostic markers and often detectable years before disease manifestation. They are also detectable in quartz dust exposed individuals.

T-cell receptor (TCR). Antigen specific receptor on T-cells composed of one set of heterodimeric chains. Two types of TCR heterodimers are known (α/β and γ/δ). Functional binding for TCR requires a complex of major histocompatibility complex, antigenic peptide and TCR.

Th0-cells. Subpopulation of helper T-lymphocytes with a less restricted cytokine profile than Th1 and Th2 cells. Th0-like responses are observed in patients with rheumatoid arthritis, Sjögren's syndrome and Graves' disease.

Th1-cells. Subpopulation of helper T-lymphocytes producing mainly IL-2, IFN-γ and TNF-β, thereby responsible for phagocyte-dependent host responses. Th1 dominated responses are seen in autoimmune diseases, in which cytotoxic T cells and macrophages play a major role, e.g. multiple sclerosis, diabetes mellitus type 1, Hashimoto's thyroiditis, and Crohn's disease. Interestingly, switching from Th1 to Th2 response can prevent Th1-mediated tissue destruction in animal models.

Th2-cells. Subpopulation of ↓ helper T-lymphocytes in mice producing IL-4, IL-5, IL-6, IL-9, IL-10, IL-13. Beside other effects they provide optimal help for antibody responses. Th2 responses should also be regarded as an important downregulatory mechanism for exaggerated Th1 responses. Predominant Th2 cytokine profile is observed in patients with atopic disorders and Graft versus host disease.

Thrombocytopenia. Amount of thrombocytes below normal values. Frequently detected in patients with autoimmune diseases (e.g., ↓ systemic lupus erythematosus, ↓ Sjögren's syndrome, ↓ mixed connective tissue disease, ↓ antiphospholipid syndrome). Primary forms may be drug-induced (↓ heparin-induced thrombocytopenia) or mediated by antiplatelet antibodies (↓ idiopathic thrombocytopenic purpura).

Thyroglobulin (TG). This glycoprotein secreted by thyroid follicular cells is a major autoantigen in autoimmune thyroid diseases. **TG autoantibodies** were found in patients with autoimmune thyroiditis and Graves' disease.

Thyroiditis, autoimmune. Inflammatory destruction of the thyroid gland (ranging from a mild focal thyroiditis to extensive lymphocytic infiltration and scarring) often associated with goiter and hypothyroidism. The most common types of autoimmune thyroiditis are Hashimoto's disease and atrophic thyroiditis (primary myxedema). Autoantibodies directed to thyroid peroxidase (TPO) and thyroglobulin (TG) are found, often at very high levels, in most of these patients. Several cell- and autoantibody-mediated mechanisms (e.g., ↓ cytotoxic T-lymphocytes, complement-mediated lysis, alteration of target cell function, ↓ antibody-dependent cell-mediated cytotoxicity) contribute to the inflammatory thyroid injury. Autoimmune thyroiditis occurs spontaneously (↓ spontaneous autoimmune thyroiditis) or can be induced experimentally in animals (↓ experimental autoimmune thyroiditis).

Thyroid peroxidase (TPO). This thyroid enzyme is a major autoantigen in autoimmune thyroid diseases. **TPO autoantibodies** were found in patients with autoimmune thyroiditides and Graves' disease.

Thyroid-stimulating hormone receptor (TSH-R). Main autoantigenic target in patients with graves' disease. Most **TSH-R autoantibodies** are stimulatory acting as agonists of TSH, but also receptor blocking antibodies were found.

Tissue transglutaminase (tTG). Main target of autoantibodies in ⟨ celiac disease.

T-lymphocytes (T-cells). Thymus-dependent lymphocytes which differentiate in the thymus to express ⟨ T-cell receptor molecules (TCRs) that are specifc for complexes comprising short peptides bound to and presented by ⟨ major histocompatibility complex (MHC) molecules. Different subpopulations of regulatory and effector cells, see ⟨ cytotoxic, ⟨ helper, ⟨ regulatory and ⟨ suppressor T-cells.

Tolerance. Persistent condition of specific immunological unresponsiveness, resulting from previous non-sensitizing exposure to the antigen. See also: ⟨ self-tolerance.

Urticaria. Transient eruption of skin characterized by erythematous or oedematous swelling (wheal) of the dermis or subcutaneous tissue.

Vasculitis. Acute or chronic inflammation of the vessel walls that can lead to necrosis, fibrosis or thrombosis. Autoimmunity plays an important role in some vasculitides (e.g., ⟨ ANCA-associated vasculitides, ⟨ Goodpasture's disease, ⟨ cryoglobulinemic vasculitis).

Vetoing. Elimination (⟨ apoptosis) of the self-peptide-MHC complex recognizing lymphocyte by the self-peptide presenting (veto) cell. A less important regulatory mechanis of ⟨ self-tolerance.

Warm autoantibody type. Autoantibodies that react optimally at higher temperatures (37^0C) with surface antigens of red blood cells. They mediate autoimmune haemolytic anemia.

Wegener's granulomatosis (WG). Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.

Xenobiotics. Drugs and environmental pollutants that influence immune responses (immune regulation) and may lead to autoimmunity.

14. REFERENCES

Abaitua Borda I, Philen RM, Posada de la Paz M, Gomez de la Camara A, Diez Ruiz-Navarro M, Gimenez Ribota O, Alvargonzalez Soldevilla J, Terracini B, Severiano Pena S, Fuentes Leal C, & Kilbourne EM (1998) Toxic oil syndrome mortality: the first 13 years. Int J Epidemiol, **27**: 1057-1063.

Abedi-Valugerdi M & Möller G (2000) Contribution of H-2 and non-H-2 genes in the control of mercury-induced autoimmunity. Int Immunol, **12**(10): 1425-1430.

Abraham JE, Svare CW, & Frank CW (1984) The effect of dental amalgam restorations on blood mercury levels. J Dent Res, **63:** 71-73.

Adachi Y, Bradford BU, Gao W, Bojes, HK & Thurman RG (1994) Inactivation of Kuppfer cells prevents early alcohol-induced liver injury. Hepatology, **20**: 453-460.

Agnotti C (2004) Immunology of cutaneous lupus erythematosis. Clin Dermatol, **22**: 105-112.

Aguilera I, Wichmann IJ, Sousa M, Bernados A, Franco E, Garcia-Lozano JR, Nunez-Roldan A. (2001) Antibodies against glutathione S-transferase T1 (GSTT1) in patients with de novo immune hepatitis following liver transplantation. Clin Exp Immunol, **26**: 535-539.

Aida T et al. (1998) Evaluation of allergenic potential of low-molecular compounds by mouse popliteal lymph node assay. J Toxicol Sci, **23**(5): 425-432.

Aikoh T, Tomokuni A, Matuskii T, Hyodoh F, Ueki H, Otsuki T, & Ueki A (1998) Activation – induced cell death in human peripheral blood lymphocytes after stimulation with silicate *in vitro*. Int J Oncol, **12**: 1355-1359.

Alarcon GS, Roseman J, Bartolucci AA, Friedman AW, Moulds JM, Goel N, Straaton KV, & Reveille JD (1998) Systemic lupus erythematosus in three ethnic groups: II. Features predictive of disease activity early in its course. LUMINA Study Group. Lupus in minority populations, nature versus nurture. Arthritis Rheum, **41**(7): 1173-1180.

Alarcon-Segovia D & Alarcon-Riquelme M (1989) Autoimmune reactions in humans induced by diphenylhydantoin and nitrofurantoin. In: Kammuller MD, Bloksma N, & Seinen W eds. Autoimmunity and toxicology: Immune disregulation induced by drugs and chemicals, pp 151-166.

Albano SA, Santana-Sahagun E, & Weisman MH (2001) Cigarette smoking and rheumatoid arthritis. Semin Arthritis Rheum, **31**(3): 146-159.

Albano E (2002) Free radical mechanisms in immune reactions associated with alcoholic liver disease. Free Radic Biol Med, **32**: 110-114.

Albers R et al. (1997) The use of reporter antigens in the popliteal lymph node assay to assess immunomodulation by chemicals. Toxicol Appl Pharmacol, **143**(1): 102-109.

Albers R et al. (1998) Selective immunomodulation by the autoimmunity-inducing xenobiotics streptozotocin and HgCl2. Eur J Immunol, **28**(4): 1233-1242.

Aldridge WN (1992) The Toxic oil syndrome (Toxic oil syndrome, 1981): from the disease towards a toxicological understanding of its chemical aetiology and mechanism. Toxicol Lett, **64/65**: 59-70.

Alonso-Ruiz A, Calabozo M, Perez-Ruiz F, & Mancebo L (1993) Toxic oil syndrome. A long-term follow-up of a cohort of 332 patients. Medicine (Baltimore), **72**: 285-295.

Alvarez-Nemegyei J, Cobarrubias-Cobos A, Escalante-Triay F, Sosa-Muñoz J, Miranda JM, & Jara LJ (1998) Bromocriptine in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled study. Lupus, **7**: 414-419.

Amino N, Izumi Y, Hidaka Y, Takeoka K, Nakata Y, Tatsumi KI, Nagata A, & Takano T (2003) No increases of blocking type anti-thyrotropin receptor antibodies during pregnancy in patients with Graves' disease. J Clin Endocrinol Metab, **88**: 5871-5874.

Anaya JM, Correa PA, Herrera M, Eskdale J, & Gallagher G (2002) Interleukin 10 (IL-10) influences autoimmune response in primary Sjögren's syndrome and is linked to IL-10 gene polymorphism. J Rheumatol, **29**: 1874-1876.

Anderton SM (2004) Post-translational modifications of self antigens: implications for autoimmunity. Curr Opin Immunol, **16**: 753-758.

Andrade F, Casciola-Rosen L, & Rosen A (2000) Apoptosis in systemic lupus erythematosus: Clinical implications. Rheum Dis Clin North Am, **26**: 215-227.

Andre F, Gillon F, Andre C, Lafont S, & Jourdan G (1983) Pesticide-containing diets augment anti-sheep red blood cell nonreaginic antibody responses in mice but may prolong murine infection with *Giardia muris*. Environ Res, **32**: 145-154.

Andre M, Canon JL, Levecque P, Dermine P, Mortier C, & Leveau F (1991) Eosinophilia-Myalgia syndrome associated with L-tryptophan: A case report with pulmonary manifestations and review of the literature. Acta Clin Belg, **46** : 178-182.

Angell M (1997) Antipolymer antibodies, silicone breast implants, and fibromyalgia . Lancet, **349**: 1171-1172 (Letter).

Aractingi S & Khosrotehrani K (2005) Microchimerism: Fears and hopes. Dermatology, **210**: 1-2.

Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, & Harley JB (2003) Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med, **349**(16): 1526-1533.

Arepalli SR, Bezabeh S, & Brown SL (2002) Allergic reactions to platinum in silicone breast implants. J Long Term Eff Med Implants, **12**: 299-306.

Arnaiz-Villena A, Vicario J L, Serrano-Rios M, Bellas C, & Mampaso F (1982) Glomerular basement-membrane antibodies and HLA-DR2 in Spanish rapeseed oil disease. N Engl J Med, **307**: 1404-1405.

Arnett FC & Moulds JM (1991) HLA class III molecules and autoimmune rheumatic diseases. Clin Exp Rheumatol, **9**: 289-296.

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al. (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum, **31**: 315-324.

Artlett, CM, Smith JB, & Jimenez SA (1998) Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. N Engl J Med, **338**: 1186-1191.

Arnett FC, Reveille JD, Goldstein R et al. (1996) Autoantibodies to fibrillarin in systemic sclerosis (scleroderma). An immunogenetic, serologic, and clinical analysis. Arthrits Rheum, **39**: 1151-1160.

Arnett FC, Fritzler MJ, Ahn C, & Holian A (2000) Urinary mercury levels in patients with autoantibodies to U3-RNP (fibrillarin). J Rheumatol, **27**(2)**:** 405-410.

Artlett CM, Ramos R, Jimenez SA, Patterson K, Miller FW, & Rider LG (2000) Chimeric cells of maternal origin in juvenile inflammatory myopathies. Lancet, **356**: 2155-2156.

Ascherio A, Munger KL, Lennette ET, Spiegelman D, Hernan MA, Olek MJ, Hankinson SE, & Hunter DJ (2001) Epstein-Barr virus antibodies and risk of multiple sclerosis: a prospective study. J Am Med Assoc, **286**: 3083-3088.

Asseman C & von Herrath M (2002) About $CD4^{pos}$ $CD25^{pos}$ regulatory cells. Autoimmunity Rev, **1**: 190-197.

Aten J et al. (1988) Mercuric chloride-induced autoimmunity in the brown Norway rat. Cellular kinetics and major histocompatibility complex antigen expression. Am J Pathol, **133**(1): 127-138.

Aten J et al. (1991) Susceptibility to the induction of either autoimmunity or immunosuppression by mercuric chloride is related to the major histocompatibility complex class II haplotype. Eur J Immunol, **21**(3): 611-616.

Atkinson MA & Eisenbarth GS (2001) Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet, **358**: 221-229.

ATSDR (1997) Toxicological profile for vinyl chloride. Atlanta, Georgia, US Department of Health and Human Services, Public Health Service, Agency for Toxic Substance and Disease Registry, 277 pp.

Aucoin … (1989) Propylthiouriacil-induced immune mediated disease syndrome in the cat: a novel model for a drug-induced lupus-like disease. In: Kammuller ME, Bloksma N, & Seinen W, eds Autoimmunity and toxicology immune disregulation induced bydrugs and chemicals, pp. 309-320.

Ayer LM, Edworthy SM, & Fritzler MJ (1993) Effect of procainamide and hydralazine on poly (ADP-ribosylation) in cell lines. Lupus, **2**(3): 167-172.

Bachmann M (2004) Novel autoimmune models: Lessons from recent transgenic and knock in animals. In: Conrad K, Bachmann M, Chan EKL, Fritzler MJ, Humbel RL, Sack U, & Shoenfeld Y ed. From animal models to human genetics. Lengerich, Pabst Science Publishers, pp 24-42.

Bachmann M, Tröster H, Bartsch H, & Grölz D (1996) A frame shift mutation in a hot spot of the nuclear autoantigen La/SS-B. J Autoimmun, **9**: 747-756.

Bachot N & Roujeau JC (2001) Physiopathology and treatment of severe drug eruptions. Curr Opin Allergy Clin Immunol, **1**(4): 293-298.

Bagchi, N et al. (1990) Antioxidants delay the onset of thyroiditis in obese strain chickens. Endocrinology, **127**(4): 1590-1595.

Bagenstose LM, Salgame P, & Monestier M (1998a) Mercury-induced autoimmunity in the absence of IL-4. Clin Exp Immunol, **114**: 9-12.

Bagenstose LM, Salgame P, & Monestier M (1998b) IL-12 Down-regulates autoantibody production in mercury-induced autoimmunity. J Immunol, **160**: 1612-1617.

Bagenstose LM, Salgame P, & Monestier M (1999a) Murine mercury-induced autoimmunity: a model of chemically related autoimmunity in humans. Immunol Res, **20**(1): 67-78.

Bagenstose LM, Salgame P, & Monestier M (1999b) Cytokine regulation of a rodent model of mercury chloride-induced autoimmunity. Environ Health Perspect, **107**(Suppl 5): 807-810.

Bagenstose LM, Mentink-Kane MM, Brittingham A, Mosser DM, & Monestier M (2001) Mercury enhances susceptibility to murine leishmaniasis. Parasite Immunol, **23**(12): 633-640.

Bagenstose LM, Class R, Salgame P, & Monestier M (2002) B7-1 and B7-2 co-stimulatory molecules are required for mercury-induced autoimmunity. Clin Exp Immunol, **127**(1): 12-19.

Bagheri MM, Alagheband M, Memar OM, & Eiler DB (2002) Pemphigus foliaceus presenting as eruptive seborrheic keratosis and responding to oral gold treatment. J Drug Dermatol, **1**: 333-334.

Baird DD, Wilcox AJ, & Herbst AL (1996) Self-reported allergy, infection, and autoimmune diseases among men and women exposed *in utero* to diethylstilbestrol. J Clin Epidemiol, **49**: 263-266.

Balazs T (1987) Immunogenetically controlled autoimmune reactions induced by mercury, gold and D-penicillamine in laboratory animals: a review from the vantage point of premarketing safety studies. Toxicol Ind Health, **3**(3): 331-336.

Balazs T & Robinson CJ (1983) Procainamide-induced antinuclear antibodies in beagle dogs. Toxicol Appl Pharmacol, **71**(2): 299-302.

Ball JA & Young KR Jr (1998) Pulmonary manifestations of Goodpasture's syndrome. Antiglomerular basement membrane disease and related disorders. Clin Chest Med, **19**: 777-791 (ix).

Bardin I, Dryll A, & Debeyre N (1982) HLA system and side effects of gold and D-penicillamine teatment of rheumatoid arthritis. Ann Rheum Dis, **41**: 599-601.

Barendrecht MM et al. (2002) Susceptibility to cyclosporin A-induced autoimmunity: strain differences in relation to autoregulatory T cells. J Autoimmun, **18**(1): 39-48.

Barnett JB, Barfield L, Walls R, Joyner R, Owens R, & Soderberg LS (1987) The effect of in utero exposure to hexachlorobenzene on the developing immune response of BALB/c mice. Toxicol Lett, **39**: 263-274.

Barth H, Klein R, & Berg PA (2001) L-tryptophan contaminant "peak E" induces the release of IL-5 and IL-10 by peripheral blood mononuclear cells from patients with functional somatic syndromes. Clin Exp Immunol, **126**: 186-192.

Bataller R, North KE, & Brenner DA (2003) Genetic polymorphisms and the progression of liver fibrosis: A critical appraisal. Hepatology, **37**: 493-503.

Bates MN, Fawcett J, Garrett N, *et al*. (2004) Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol, **33:** 1-9.

Beech JT et al. (1997) CD4+ Th2 cells specific for mycobacterial 65-kilodalton heat shock protein protect against pristane-induced arthritis. J Immunol, **159**(8): 3692-3697.

Beekman WH, Feitz R, Van Diest PJ, & Hage JJ (1997) Migration of silicone through the fibrous capsules of mammary prostheses. Ann Plast Surg, **38**: 441-445.
Bell SA (1996) The Toxic oil syndrome: An example of an exogenously induced autoimmune reaction. Mol Biol Rep, **23**: 261-263.

Bell SA, Hobbs MV, & Rubin RL (1992) Isotype-restricted hyperimmunity in a murine model of the Toxic oil syndrome. J Immunol, **148**: 3369-3376.

Bell SA, Sander C, Kuntze I, & Chatelain R (1999) The acute pathology of fatty acid anilides and linoleic diester of 3-phenylamino-1,2-propanediol in mice: Possible implication as aetiologic agents for the Toxic oil syndrome. Arch Toxicol, **73**: 493-495.

Bell SA, Kuntze I, Caputo A, & Chatelain R (2002) Strain-dependent *in vitro* and *in vivo* effects of oleic acid anilides on splenocytes and T cells in a murine model of the Toxic oil syndrome. Food Chem Toxicol, **40**: 19-24.

Belluzzi A (2002) N-3 fatty acids for the treatment of inflammatory bowel diseases. Proc Nutr Soc, **61**: 391-395.

Ben-Ari Z & Czaja AJ (2001) Autoimmune hepatitis and its variant syndromes. Gut, **49**: 589-594.

Bennett ST, Lucassen AM, Gough SC, Powell EE, Undlien DE, Pritchard LE, Merriman ME, Kawaguchi Y, Dronsfield MJ, Pociot F. (1995) Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. Nat Genet, **9**: 284-292.

Bennett CL, Christie P, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, & Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet, **27**: 20-21.

Ben-Nun A & Cohen IR (1982) Experimental autoimmune encephalomyelitis (EAE) mediated by T cell lines: process of selection of lines and characterization of the cells. J Immunol, **129**(1): 303-308.

Berger BD, Acton RT, Koopman WJ, & Alarcon GS (1984) DR antigens and gold toxicity in white rheumatoid arthritis patients. Arthritis Rheum, **27**: 601-607.

Berger T, Rubner P, Schautzer F, Egg R, Ulmer H, Mayringer I, Dilitz E, Deisenhammer F, & Reindl M (2003) Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med, **349**: 139-145.

Berking C, Hobbs MV, Chatelain R, Meurer M, & Bell SA (1998) Strain-dependent cytokine profile and susceptibility to oleic acid anilide in a murine model of the Toxic oil syndrome. Toxicol Appl Pharmacol, **148**: 222-228.

Bernard A, Roels H, Hubermont G, Buchet JP, Masson PL, & Lauwerys R (1976) Characterization of the proteinuria in cadmium exposed workers. Int Arch Occup Environ Health, **38**: 19-30.

Bernard A, Lauwerys R, Gengoux P, Mahieu P, Foidart JM, Druet P, & Weening JJ (1984) Anti-laminin antibodies in Sprague-Dawley and Brown Norway rats chronically exposed to cadmium. Toxicology, **31**: 307-313.

Bernard A, Roels HR, Foidart JM, & Lauwerys RL (1987) Search for anti-laminin antibodies in the serum of workers exposed to cadmium, mercury vapour or lead. Int Arch Occup Environ Health, **59**: 303-309.

Bernier J, Girard D, Krzystyniak K, Chevalier G, Trottier B, Nadeau D, Rola-Pleszczynski M, & Fournier M (1995) Immunotoxicity of aminocarb : III. Exposure route-dependent immunomodulation by aminocarb in mice. Toxicology, **99**: 135-146.

Betterle C, Dal Pra C, Mantero F, & Zanchetta R (2002) Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocrinol Rev, **23**: 327-364.

Bi WF, Wang YS, Huang MY, & Meng DS (1985) Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Safety, **10**: 281-289.

Bigazzi P (1994) Autoimmunity and heavy metals. Lupus, **3**: 449-453.

Bigazzi PE (1999a) Mercury inducing disease in animal experiments. Environ Health Perspect, **107**(Suppl 5): 753-765.

Bigazzi PE (1999b) Metals and kidney autoimmunity. Environ Health Perspect, **107**(Suppl 5): 753-765.

Bingley PJ, Bonifacio E, Williams AJ, Genovese S, Bottazzo GF, & Gale EA (1997) Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes, **46**: 1701-1710.

Birkefeld AB, Bertermann R, Eckert H, & Pfleiderer B (2003) Liquid and solid-state high resolution NMR methods for the investigation of aging processes of silicone breast implants. Biomaterials, **24**: 35-46.

Black J (1999) The puzzle of pink disease. J R Soc Med, **92:** 478-491.

Black CM, Welsh KO, Walker AE, Bernstein RM, Catoggio LJ, McGregor AR, & Jones JK (1983) Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. Lancet, **1**(8314-15): 53-55.

Black C, Pereira S, McWhirter A, Welsh K, & Laurent R (1986) Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. J Rhematol, **13**: 1059-1062.

Blair PB (1992) Immunologic studies of women exposed *in utero* to diethylstilbestrol. In: Colborn T & Clement C eds. Chemically-induced alterations in sexual and functional development: the wildlife/human connection. Princeton, Princeton Scientific Publishing Co, pp 289-293.

Blair PB, Noller KL, Turiel J, Forghani B, & Hagens S (1992) Disease patterns and antibody responses to viral antigens in women exposed *in utero* to diethylstilbestrol. In: Colborn T & Clement C eds. Chemically-induced alterations in sexual and functional development: the wildlife/human connection. Princeton, Princeton Scientific Publishing Co., pp 283-288.

Blank M, Krause I, Buskila D, Teitelbaum D, Kopolovic J, Afek A, Goldberg I, & Shoenfeld Y (1995) Bromocriptine immunomodulation of experimental SLE and primary antiphospholipid syndrome via induction of nonspecific T suppressor cells. Cell Immunol, **162**: 114-122.

Blauvelt A, Hwang ST, & Udey MC (2003) 11. Allergic and immunologic diseases of the skin. J Allergy Clin Immunol, **111**: S560-S570.

Blaylock BL, Hollady SD, Comment CE, Heindel JJ, & Luster MI (1992) Modulation of perinatal thymocyte surface antigen expression and inhibition of thymocyte maturation by exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Toxicol Appl Pharmacol, **112**: 207-213.

Bloksma N et al. (1994) Long-term treatment with 5,5-diphenylhydantoin reduces lymphadenopathy and anti-ssDNA autoantibodies in C57BL/6-lpr/lpr mice. Int J Immunopharmacol, **16**(3): 261-268.

Bloksma N et al. (1995) Predictive immunotoxicological test systems: suitability of the popliteal lymph node assay in mice and rats. Crit Rev Toxicol, **25**(5): 369-396.

Blossom S, Pumford NR, & Gilbert KM (2004) Activation and attenuation of apoptosis of CD4+ T cells following *in vivo* exposure to two common environmental toxicants, trichloroacetaldehyde hydrate and trichloroacetic acid. J Autoimmun, **23**: 211-220.

Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, & Bell H (1998) Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol, **33**(1): 99-103.

Bodeutsch C, de Wilde PC, Kater L, van Houwelingen JC, van den Hoogen FH, Kruize AA, Hene RJ, van de Putte LB, & Vooijs GP (1992) Quantitative immunohistologic criteria are superior to the lymphocytic focus score criterion for the diagnosis of Sjogren's syndrome. Arthritis Rheum, **35**: 1075-1087.

Bogliun G & Beghi E (2004) Incidence and clinical features of acute inflammatory polyradiculoneuropathy in Lombardy, Italy, 1996. Acta Neurol Scand, **110**(2): 100-106.

Boisseau-Garsaud AM, Garsaud P, Cales-Quist D, Helenon R, Queneherve C, & Claire RC (2000) Epidemiology of vitiligo in the French West Indies (Isle of Martinique). Int J Dermatol, **39**(1): 18-20.

Bondurant S, Ernster V, & Herdman R eds. (1999) Committee on the Safety of Silicone Breast Implants. Washington, DC, The National Academies Press, National Academy of Sciences.

Borel JF et al. (1976) Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions, **6**(4): 468-475.

Borel JF et al. (1977) Effects of the new anti-lymphocytic peptide cyclosporin A in animals. Immunology, **32**(6): 1017-1025.

Bottazzo GF, Florin-Christensen A, & Doniach D (1974) Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet, **2**: 1279-1283.

Botto M (2001) Links between complement deficiency and apoptosis. Arthritis Res, **3**: 207-210.

Bouma G & Strober W (2003) The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol, **3**: 521-533.

Boumpas DT, Fessler BJ, Austin HA 3rd, Balow JE, Klippel JH, & Lockshin MD (1995) Systemic lupus erythermatosus: emerging concepts. Part 2: Dermatologic and joint disease, the antiphospholipid antibody syndrome, pregnancy and hormonal therapy, morbidity and mortality, and pathogenesis. Ann Intern Med, **123**: 42-53.

Bovenzi M, Barbone F, Betta A, Tommasini M, & Versini W (1995) Scleroderma and occupational exposure. Scand J Work Environ Health, **21**: 289-292.

Bovenzi M, Barbone F, Pisa FE, Betta A, Romeo L, Tonello A, Biasis D, & Caramaschi P (2004) A case-control study of occupational exposures and systemic sclerosis. Int Arch Occup Environ Health, **77**: 10-16.

Bowness P (2002) HLA B27 in health and disease: a double-edged sword? Rheumatology, **41**: 857-868.

Boyton RJ & Altmann DM (2002) Transgenic models of autoimmune disease. Clin Exp Immunol, **127**(1): 4-11.

Bradley SG, White KL Jr, McCay JA, Brown RD, Musgrove DL, WIlson S, Stern M, Luster MI, & Munson AE (1994a) Immunotoxicity of 180 day exposure to polydimethylsiloxane (silicone) fluid, gel and elastomer and polyurethane disks in female B6C3F1 mice. Drug Chem Toxicol, **17**: 221-269.

Bradley SG, Munson AE, McCay JA, Brown RD, Musgrove DL, Wilson S, Stern M, Luster MI, & White KL (1994b) Subchronic 10 day immunotoxicity of polydimethylsiloxane (silicone) fluid, gel and elastomer and polyurethane disks in female B6C3F1 mice. Drug Chem Toxicol, **17**: 175-220.

Brandon HJ, Jerina KL, Wolf CJ, & Young VL (2003) Biodurability of retrieved silicone gel breast implants. Plast Reconstr Surg, **111**: 2295-2306.

Brantley SK, Davidson SF, Arnold PA, Johnson MB, Talbot PJ, Grogan JB, Cuchens MA, Hsu HS, & Das SK (1990) Assessment of the lymphocyte responses to silicone Plast Reconstr Surg, **86**: 1131-1137.

Brennan P, Hajeer A, Ong KR, Worthington J, John S, Thomson W, Silman A, & Ollier B (1997) Allelic markers close to prolactin are associated with HLA-DRB1 susceptibility alleles among women with rheumatoid arthritis and systemic lupus erathematosus. Arthritis Rheum, **40**: 1383-1386.

Bridges ED, Greenstein BD, Khamashta MA, & Hughes GR (1993) Specificity of estrogen receptors in rat thymus. Int J Immunopharmacol, **15**: 927-932.

Bridges AJ, Anderson JD, Burns DE, Kemple K, Kaplan JD, & Lorden T (1996) Autoantibodies in patients with silicone implants. Curr Top Microbiol Immunol, **210**: 277-282..

Brik R et al. (1995) D-penicillamine-induced autoantibodies in a mouse model. Clin Exp Rheumatol, **13**(4): 483-488.

Brostoff J, Blanca M, Boulton P, & Serrano S (1982) Absence of specific IgE antibodies in Toxic oil syndrome. Lancet, Jan 30;1(8266):277.

Broughton A, Thrasher JD, & Madison R (1990) Chronic health effects and immunological alterations associated with exposure to pesticide. Comments Toxicol, **4**: 59-71.

Brouwer A, Longnecker MP, Birnbaum LS, Cogliano J, Kostyniak P, Moore J, Schantz S, & Winneke G (1999) Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ Health Perspect, **107**(Suppl 4): 639-649.

Brown SL (2002) Epedemiology of silicone breast implants. Epidemiology, **13**: S34-S39.

Brown TR et al. (1991) Uptake and metabolism of iodine is crucial for the development of thyroiditis in obese strain chickens. J Clin Invest, **88**(1): 106-111.

Brown LM, Gridley G, Olsen JH, Mellemkjaer L, Linet MS, & Fraumeni JF (1997a) Cancer risk and mortality patterns among silicotic men in Sweden and Denmark. J Occup Environ Med, **66**: 323-333.

Brown SL, Silverman BG, & Berg WA (1997b) Rupture of silicone-gel breast implants: causes, sequelae, and diagnosis. Lancet, **350**: 1531-1537.

Brown SL, Middleton MS, Berg WA, Soo MS, & Pennello G (2000) Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. Am J Roentgenology, **175**: 1057-1064.

Brown SL, Pennello G, Berg WA, Soo MS, & Middleton MS (2001) Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. J Rheumatol, **28**: 996-1003.

Brown JM, Archer AJ, Pfau JC, & Holian A (2003) Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice. Clin Exp Immunol, **131**(3): 415-421.

Brownlie BE & Wells JE (1990) The epidemiology of thyrotoxicosis in New Zealand: incidence and geographical distribution in North Canterbury, 1983-1985. Clin Endocrinol (Oxford), **33**(2): 249-259.

Brennan P, Hajeer A, Ong KR, Worthington J, John S, Thomson W, Silman A, & Ollier B (1997) Allelic markers close to prolactin are associated with HLA-DRB1 susceptibility alleles among women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum, **40**: 1383-1386.

Brik R et al. (1995) D-penicillamine-induced autoantibodies in a mouse model. Clin Exp Rheumatol, **13**(4): 483-488.

Bruining GJ, Molenaar JL, Grobbee DE, Hofman A, Scheffer GJ, Bruining HA, de Bruyn AM, & Valkenburg HA (1989) Ten-year follow-up study of islet-cell antibodies and childhood diabetes mellitus. Lancet, **1**: 1100-1103.

Brun JG, Madland TM, & Vedeler CA (2002) Immunoglobulin G Fc-receptor (Fcγ R) IIA, IIIA, and IIIB polymorphisms related to disease severity in rheumatoid arthritis. J Rheumatol, **29**: 1135-1140.

Burns CJ, Laing TJ, Gillespie BW, Heeringa SG, Alcser KH, Mayes MD, Wasko MC, Cooper BC, Garabrant DH, & Schottenfeld D (1996) The epidemiology of scleroderma among women: assessment of risk from exposure to silicone and silica. J Rheum, **23**: 1904-1911.

Caforio AL, Mahon NJ, Tona F, & McKenna WJ (2002) Circulating cardiac autoantibodies in dilated cardiomyopathy and myocarditis: pathogenetic and clinical significance. Eur J Heart Fail, **4**: 411-417.

Calder PC (1997) n-3 polyunsaturated fatty acids and cytokine production in health and disease. Ann Nutr Metab, **41**: 203-234.

Calemine JB, Gogal RM Jr, Lengi A, Sponenberg P, & Ahmed SA (2002) Immunomodulation by diethylstilbestrol is dose and gender related: effects on thymocyte apoptosis and mitogen-induced proliferation. Toxicology, **178**: 101-118.

Calkins BM (1989) A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci, **34**: 1841-1854.

Calvert GM, Rice FL, Boiano JM, Sheehy JW, & Sanderson WT (2003) Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med, **60**(2): 122-129.

Cam C (1958) Cases of skin porphyria related to hexachlorobenzene intoxication. Saglik Dergisi, **32**: 215-216.

Cam C (1960) Une nouvelle dermatose épidémique des enfants. Anales Dermatol, **87**: 393-397.

Cantagrel A, Navaux F, Loubet-Lescoulié P, Nourhashemi F, Enault G, Abbal M, Constantin A, Laroche M, & Maziéres B (1999) Interleukin-1ß, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms. Relationship to occurence and severity of rheumatoid arthritis. Arthritis Rheum, **42**: 1093-1100.

Cardaba B, Enzendam J, Gallardo S, del Poza V, Izquierdo Martinez M, Martin C, Cortegano MI, Aceituno E, Rojo M, Arrieta I, Palomino P, Posada de la Paz M, & Lahoz C (1999) DR2 antigens are associated with severity of disease in Toxic oil syndrome (TOS). Tissue Antigens, **55**: 110-117.

Carr L, Ruther E, Berg PA, & Lehnert H (1994) Eosinophilia-Myalgia syndrome in Germany: an epidemiologic review. Mayo Clin Proc, **69**: 620-625.

Carr LG, Hartleroad JY, Liang Y, Mendenhall C, Moritz T, & Thomasson H (1995) Polymorphism at the P450Iie1 locus is not associated with alcoholic liver disease in Caucasian men. Alcohol Clin Exp Res, **19**: 182-184.

Casciola-Rosen L, Wigley F & Rosen A (1997) Scleroderma autoantigens are uniquely fragmented by metal-catalyzed oxidation reactions: implications for pathogenesis. J Exp Med, **185**: 71-79.

Castano P (1971) Chronic intoxication by cadmium experimentally induced in rabbits. A study of kidney ultrastructure. Path Microbiol, **37**: 280-301.

Castranova V, Vallyathan V, Ramsey DM, McLaurin JL, Pack D, Leonard S, Barger MW, Ma JY, Dalal NS, & Teass A (1997) Augmentation of pulmonary reactions to quartz inhalation by trace amounts of iron-containing particles. Environ Health Perspect, **105**(Suppl 5): 1319-1324.

Cerhan JR, Saag KG, Merlino LA, Mikuls TR, & Criswell LA (2003) Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol, **157**: 345-354.

Chan OT, Madaio MP, & Shlomchik MJ (1999) The central and multiple roles of B cells in Lupus pathogenesis. Immunol Rev, **169**: 107-121.

Charmley P, Nepom BB, & Concannon P (1994) HLA and T cell receptor ß-chain DNA polymorphisms identify a distinct subset of patients with pauciarticular-onset juvenile rheumatoid arthritis. Arthritis Rheum, **37**: 685-701.

Chen M, Hemmerich P, & Von Mikecz A (2002) platinum-induced autoantibodies target nucleoplasmic antigens related to active transcription. Immunobiology, **206**: 474-483.

Chenuaud P et al. (2004) Autoimmune anemia in macaques following erythropoietin gene therapy. Blood, **103**(9): 3303-3304.

Chernajovsky Yet al. (2000) Immuno- and genetic therapy in autoimmune diseases. Genes Immun, **1**(5): 295-307.

Chiang SY, Swenberg JA, Weisman WH, & Skopek TR (1997) Muatagenicity of vinyl chloride and its reactive metabolites, chloroethylene oxide and chloroacetaldehyde, in a metabolically competent human B-lymphoblastoid line. Carcinogenesis, **18**: 31-36.

Choquet-Kastylevsky G, Vial T, & Descotes J (2001) Drug allergy diagnosis in humans: possibilities and pitfalls. Toxicology, **158**: 1-10.

Christner PJ, Artlett CM, Conway RF, & Jimenez SA (2000) Increased numbers of microchimeric cells of fetal origin are associated with dermal fibrosis in mice following injection of vinyl chloride. Arthritis Rheum, **43**: 2598-2605.

Chu JL, Drappa J, Parnassa A, & Elkon KB (1993) The defect in Fas mRNA expression in MRL/lpr mice is associated with insertion of the retrotransposon, ETn. J Exp Med, **178**: 723-730.

Ciapetti G, Granchi D, Stea S, Cenni E, Schiavon P, Giuliani R, & Pizzoferrato A (1995) Assessment of viability and proliferation of *in vivo* silicone primed lymphocytes after *in vitro* re-exposure to silicone J Biomed Mat Res, **29**:583-590.

Cines DB & Blanchette VS (2002) Immune thrombocytopenic purpura. N Engl J Med, **346**: 995-1008.

Clarkson TW (2002) The three modern faces of mercury. Environ Health Perspect, **110**(Suppl.1): 11-23.

Clarkson TW, Magos L, & Myers GJ (2003) The toxicology of mercury-current exposures and clinical manifestations. N Engl J Med, **349:** 1731-1737.

Clot P, Albano E, Eliasson E, Tabone M, Arico S, Israel Y, Moncada C, Ingelman-Sundberg M. (1996) Cytochrome P4502E1 hydroxyethyl radical adducts as the major antigen in autoantibody formation among alcoholics. Gastroenterology, 111(1):206-16.

Collis N & Sharpe DT (1998) Correspondence. Rupture of silicone gel implants. Lancet, **351**: 520.

Colosio C, Maroni M, Barcellini W, Meroni P, Alcini D, Colombi A, Cavallo D, & Foa V (1993) Toxicological and immune findings in workers exposed to pentachlorophenol (PCP). Arch Environ Health, **48**(2): 81-88.

Compston A & Coles A (2002) Multiple sclerosis. Lancet, **359**: 1221-1231.

Comstock GW, Burke AE, Hoffman SC, Helzlsouer KJ, Bendich A, Masi AT, Norkus EP, Malamet RL, Gershwin ME. (1997) Serum concentrations of α tocopherol, β carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis, **56**: 323-325.

Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, & Moreau T (1998) Rate of pregnancy-related relapse in multiple sclerosis: Pregnancy in multiple sclerosis group. N Eng J Med, **339**: 285-291.

Conrad K, Melhorn J, Luthke K, Dorner T, & Frank KH (1996) Systemic lupus erythematosus after heavy exposure to quartz dust in uranium mines: clinical and serological characteristics. Lupus, **5**: 62-69.

Constant CM, Swaak AJ, Wiggers T, Wai RT, & Van Geel AN (2000) First evaluation study of the Dutch Working Party on silicone breast implants (SBI) and the silicone-related symptom complex (SRSC) Clin Rheumatol, **19**: 458-463.

Cook RR & Curtis JM (1998) Correspondence. Rupture of silicone gel implants. Lancet, **351**: 520.

Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Parks CG, & Gilkeson GS (1998) Hormonal environmental, and infectious disease risk factors for the development of systemic lupus erythematosus. Arthritis Rheum, **41**: 1714-1724.

Cooper GS, Miller FW, & Pandey JP (1999) The role of genetic factors in autoimmune disease: Implications for environmental research. Environ Health Perspect, **107**(Suppl 5): 693-700.

Cooper GS, Miller FW, & Germolec DR (2002) Occupational exposure and autoimmune diseases. Int Immuno-Parmacol, **2**: 303-313.

Cooper GS, Martin SA, Longnecker MP, Sandler DP, & Germolec DR (2004) Associations between plasma DDE levels and immunologic measures in African-American farmers in North Carolina. Environ Health Perspect, **112**: 1-5.

Corbett EL, Mozzato-Chamay N, Butterworth AE, De Cock KM, Williams BG, Churchyard GJ, & Conway DJ (2002) Polymorphisms in the tumor necrosis factor-alpha gene promoter may predispose to severe silicosis in black South African miners. Am J Respir Crit Care Med, **165**: 690-693.

Cornacchia E, Golbus J, Maybaum J, Strahler J, Hanash S, & Richardson B (1988) Hydralazine and procainamide inhibit T cell DNA methylation and induce autoreactivity. J. Immunol, **140**(7) : 2197-2200.

Costenbader KH, Kim DJ, Peerzada J, Lockman S, Nobles-Knight D, Petri M, & Karlson EW (2004) Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum, **50**: 849-857.

Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, & Kaslow RA (1996) The epidemiology of Wegener's granulomatosis: Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis Rheum, **39**(1): 87-92.

Craelius W (1978) Comparative epidemiology of multiple sclerosis and dental caries. Epidemiol Community Health, **32:** 155-165.

Craig WY, Ledue TB, Johnson AM, & Ritchie RF (1999) The distribution of antinuclear antibody titers in "normal" children and adults. J Rheum, **26**: 914-919.

Cribb AE et al. (1996) Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. Adverse Drug React Toxicol Rev, **15**(1): 9-50.

Crilly A, Hamilton J, Clark CJ, Jardine A, & Madhok R (2002) Analysis of transforming growth factor ß1 gene polymorphisms in patients with systemic sclerosis. Ann Rheum Dis, **61**: 678-681.

Cripps DJ, Peters HA, Gocmen A, & Dogramici I (1984) Porphyria turcica due to hexachlorobenzene: a 20 to 30 year follow-up study on 204 patients. Br J Dermatol, **111**: 413-422.

Crommelin DJ et al. (2003) Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Int J Pharm, **266**(1-2): 3-16.

Cuadrado JI, de Pedro-Cuesta J, Ara JR, Cemillan CA, Diaz M, Duarte J, Fernandez MD, Fernandez O, Garcia-Lopez F, Garcia-Merino A, Velasquez JM, Martinez-Matos JA, Palomo F, Pardo J, & Tobias A (2004) Public health surveillance and incidence of adulthood Guillain-Barre syndrome in Spain, 1998-1999: the view from a sentinel network of neurologists. Neurol Sci, **25**(2): 57-65.

Cuellar ML, Gluck O, Molina JF, Guttiérrez S, Garcia C, & Espinoza R (1995) silicone breast implant-associated musculoskeletal manifestations. Clin Rheumatol, **14**: 667-672.

Cuttres TW (1997) Dental amalgam and human health, current situation- a New Zealand review. In: Mjor IA & Pakomov GN eds. Dental amalgam and alternative direct restorative materials. Geneva, World Health Organization, pp 63-67.

Cutulo M, Sulli A, Capellino S, Villaggio B, Montagna P, Seriolo B, & Straub RH (2004) Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. Lupus, **13**: 635-638.

Czernielewski A, Kiee-Swierczynska M, Gluszeez, & Wozniak L (1979) Dermatological aspects of so called vinyl chloride monomer disease. Dermatosen, **27**: 108-112.

Dalakas MC & Hohlfeld R (2003) Polymyositis and dermatomyositis. Lancet, **362**: 971-982.

D'Alfonso S, Rampi M, Bocchio D, Colombo G, Scorza-Smeraldi R, & Momigliano-Richiardi P (2000) Systemic lupus erythematosus cancidate genes in the Italian population: Evidence for a significant association with interleukin-10. Arthritis Rheum, **43**: 120-128.

Dalu A, Blaydes BS, Lomax LG, & Declos KB (2000) A comparison of the inflammatory response to a polydimethylsiloxane implant in male and female Balb/c mice Biomaterials, **21**: 1947-1957.

Daly AK (1995) Molecular basis of polymorphic drug metabilism. Mol Med, **73**: 539-553.

Dambinova SA, Granstrem OK, Tourov A, Salluzzo R, Castello F, & Izykenova GA (1998) Monitoring of brain spiking activity and autoantibodies to n-terminus domain of GluR1 subunit of AMPA receptors in blood serum of rats with cobalt-induced epilepsy. J Neurochem, **71**: 2088-2093.

Damoiseaux JG (2002) Cyclosporin A-induced autoimmunity in the rat: central versus peripheral tollerance. Int J Immunopathol Pharmacol, **15**(2): 81-87.

Damoiseaux JG, Dopp EA, & Dijkstra CD (1991) Cellular binding mechanism on rat macrophages for sialylated glycoconjugates, inhibited by the monoclonal antibody ED3. J Leukoc Biol, **49**: 434-441.

Dantas DCM & Queiroz MLS (1997) Immunoglobulin E and autoantibodies in mercury-exposed. Immunopharmacol Immunotoxicol, **19**(3): 383-392.

Darnell RB & Posner JB (2003) Paraneoplastic syndromes involving the nervous system. N Engl J Med, **349**: 1543-1554.

Das P, Abraham R, & David C (2000) HLA transgenic mice as models of human autoimmune diseases. Rev Immunogenet, **2**(1): 105-114.

Das YT, Bagchi M, Bagchi D, & Preuss HG (2004) Safety of 5-hydroxy-L-tryptophan. Toxicol Let, **150:** 111-122.

David CS (1997) The mystery of HLA-B27 and disease. Immunogenetics, **46**: 73-77.

D'Cruz D (2000) Autoimmune diseases associated with drugs, chemicals and environmental factors. Toxicol Lett, **112/113**: 421-432.

Dean GS, Tyrell-Price J, Crawley J, & Isenberg DA (2000) Cytokines and systemic lupus erythematosus. Ann Rheum Dis, **59**: 243-251.

Degoul F, Sutton A, Mansouri A, Cepanec C, Degott C, Fromenty B, Beaugrand M, Valla D, & Pessayre D (2001) Homozygosity for alanine in themitochondrial targeting sequence of superoxide dismutase and risk for severe alcoholic liver disease. Gastroenterology, **120**: 1468-1474.

De Heer C, Van Driesten G, Shuurman HJ, Rozing J, & Van Loveren H (1995) No evidence for emergence of autoreactive V beta 6+ T cells in Mls-1a mice following exposure to a thymotoxic dose of 2,3,7,8- tetrachlorodibenzo-*p*-dioxin. Toxicology, **10**: 195-203.

DeHoratius RJ, Pillarisetty R, Messner RP, & Talal N (1975) Anti-nucleic acid antibodies in systemic lupus erythematosus patients and their families. Incidence and correlation with lymphocytotoxic antibodies J Clin Invest, **56**: 1149-1154.

De Jong WH, Goldhoorn CA, Kallewaard M, Geertsma RE, Van Loveren H, Bijlsma JWJ, & Schouten JSAG (2002) Study to the presence of antipolymer antibodies in a group of Dutch women with a silicone breast implant. Clin Exp Rheumatol, **20**:151-160.

De Jong WH, Kallewaard M, Goldhoorn CA, Verhoef CM, Bijlsma JWJ, Schouten JSAG, & Van Loveren H (2004) Long-term exposure to silicone breast implants does not induce antipolymer antibodies. Biomaterials, **25**: 1095-1103.

del Poza V, de Andres B, Gallardo S, Cardaba B, de Arruda-Chaves E, Cortegano MI, Jurado A, Palomino P, Oliva H, Aguilera B, Posada M, & Lahoz C (1997) Cytokine mRNA expresion in lung tissue from Toxic oil syndrome patients: a TH2 immunological mechanism. Toxicology, **118**: 61-70.

del Puente A, Knowler WC, Pettitt DJ, & Bennett PH (1988) The incidence of rheumatoid arthritis is predicted by rheumatoid factor titer in a longitudinal population study. Arthritis Rheum, **31**: 1239-1244.

Deluca HF & Cantorna MT (2001) Vitamin D: its role and uses in immunology. FASEB J, **15**: 2579-2585.

Demoly P &. Bousquet J (2001) Epidemiology of drug allergy. Curr Opin Allergy Clin Immunol, **1**(4): 305-310.

Deng C, Lu Q, Zhang Z, Rao T, Attwood J, Yung R, & Richardson B (2003) Hydralazine may induce autoimmunity by inhibitting extracellular signal-regulated kinase pathway signaling. Arthritis Rheum, **48**(3): 746-756.

Derk CT & Jimenez SA (2003) Systemic sclerosis: current views of its pathogenesis. Autoimmunol Rev, **2**: 181-191.

De Rycke L, Kruithof E, Van Damme N, Hoffman IE, Van den Bossche N, Van den Bosch F, Veys EM, & De Keyser F (2003) Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum, **48**: 1015-1023.

Descotes J (1992) The popliteal lymph node assay: a tool for studying the mechanisms of drug-induced autoimmune disorders. Toxicol Lett, **64-65**: 101-107.

Descotes J, Ravel G, & Ruat C (2002) Vaccines: predicting the risk of allergy and autoimmunity. Toxicology, **174**(1): 45-51.

Deutsch M, Tsopanou E, & Dourakis SP (2004) The autoimmune lympoproliferative syndrome (Canale-Smith) in adulthood. Clin Rheumatol, **23**: 43-44.

De Waal EJ, Schuurman H-J, Loeber JG, Van Loveren H, & Vos JG (1992) Alterations in the cortical thymic epithelium of rats after *in vivo* exposure to 2,3,7,8- tetrachlorodibenzo-*p*-dioxin (TCDD): An immunohistological study. Toxicol Appl Pharmacol, **115**: 80-88.

Dewan PA, Ashwood PJ, Rowan-Kelly B, Ferrante A, & McCallum Z (2003) The detection of IgG antibodies to silicone. Pediatr Surg, **19**: 20-24.

Dexter SL (1984) Zimeldine induced neuropathies. Hum Toxicol, **3**(2): 141-143.

DHHS (Department of Health and Human Services) (1993) Public Health Service. Dental amalgam: a scientific review and recommended Public Health Service strategy for research, education and regulation. Final report of the Subcommittee on Risk management of the Committee to Co-ordinate Environmental Health and Related Progams.

Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonissoni S, Correra A, Dianzani I, & Ramenghi U (1997) Deficiency of the Fas apoptosis pathway without gene mutations in pediatric patients with autoimmunity/lymphoproliferation. Blood, **89**: 2871-2879.

Dianzani U, Chiochetti A, & Ramenghi U (2003) Role of inherited defects decreasing Fas function in autoimmunity. Life Sci, **72**: 2803-2824.

Diggle GE (2001) The Toxic oil syndrome: 20 years on. Int J Clin Pract, **55**: 371-375.

Dijkstra CD, Dopp EA, Huitinga I, & Damoiseaux JG (1992) Macrophages in experimental autoimmune diseases in the rat: a review. Curr Eye Res, **11(**Suppl): 75-79.

Dijkstra CD, Dopp EA, Vogels IM, & Van Noorden CJ (1987) Macrophages and dendritic cells in antigen-induced arthritis. An immunohistochemical study using cryostat sections of the whole knee joint of rat. Scand J Immunol, **26**: 513-523.

Diot E, Lesire V, Guilmot JL, Metzger MD, Pilore R, Rogier S, Stadler M, Diot P, Lemarie E, Lasfargues G. (2002) Systemic sclerosis and occupational risk factors: a case-control study. Occup Environ Med, **59**(8): 545.

Dodson VN, Dinman BD, Whitehouse WM, Nasr ANM, & Magnuson HJ (1971) Occupational acroosteolysis. Arch Environ Health, **22**: 83-91.

Donker AJ, Venuto RC, Vladutiu AO, Brentjens JR, & Andres GA (1984) Effects of prolonged administration of D-penicillamine or captopril in various strains of rats. Brown Norway rats treated with D-penicillamine develop autoantibodies, circulating immune complexes, and disseminated intravascular coagulation. Clin Immunol Immunopathol, **30**(1): 142-155.

Doran MF, Pond GR, Crowson CS, O'Fallon WM & Gabriel SE (2002) Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum, **46**: 625-631.

Drappa J, Vaishnaw AK, Sullivan KE, Chu JL, & Elkon KB (1996a) The Canale Smith syndrome: an inherited autoimmune disorder associated with defective lymphocyte apoptosis. N Engl J Med, **335**: 1643-1649.

Drappa J, Vaishnaw AK, Sullivan KA, Chu JL, & Elkon KB (1996b) Fas gene mutations in the Canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. N Engl J Med, **335**: 1643-1649.

Drossaers-Bakker KW, Zwinderman AH, van Zeben D, Breedveld FC, & Hazes JM (2002) Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. Ann Rheum Dis, **61**: 405-408.

Dubey D, Kuhn J, Vial MC, Druet P, & Bellon B (1993) Anti-interleukin-2 receptor monoclonal antibody therapy supports a role for Th1 like cells in $HgCl_2$-induced autoimmunity in rats. Scand J Immunol, **37**(4): 406-412.

Dubois EL & Strain L (1972) Failure of procainamide to induce a systemic lupus erythematosus-like disease in animals. Toxicol Appl Pharmacol, **21**(2): 253-259.

Dwosh E, Guimond C, Duquette P, & Sadovnick AD (2003) The interaction of MS and pregnancy: a critical review. Int MS J, **10**: 38-42.

Edberg JE, Langefeld CD, Wu J, Moser KL, Kaufman KM, Kelly J, Bansal V, Brown WM, Salmon JE, Rich SS, Harley JB, & Kimberly RP (2002) Genetic linkage and association of Fcγ receptor IIIA (CD16A) on chromosome 1q23 with human systemic lupus erythematosus. Arthritis Rheum, **46**: 2132-2140.

Edlavitch SA (1997) Antipolymer antibodies, silicone breast implants, and fibromyalgia [letter]. Lancet, **349**: 1170.

Edworthy SM, Martin L, Barr SG, Birdsell DC, Brant RF, & Fritzler MJ (1998) A clinical study of the relationship between silicone breast implants and connective tissue disease. J Rheumatol, **25**: 254-260.

Elenkov IJ, Papanicolaou DA, Wilder RL, & Chrousos GP (1996) Modulatory effects of glucocorticoids and catecholamines on human interluekin-12 and interleukin-10 production: clinical implications. Proc Assoc Am Physicians, **108**: 374-381.

Elenkov IJ, Wilder RL, Bakalov VK, Link AA, Dimitrov MA, Fisher S, Crane M, Kanik KS, & Chrousos GP (2001) IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. J Clin Endocrinol Metab, **86**: 4933-4938.

Ellis TM, Hardt NS, Campbell L, Piacentini DA, & Atkinson MA (1997) Cellular immune reactivities in women with silicone breast implants: a preliminary investigation. Ann Allergy Asthma Immunol, **79**: 151-154.

Eltze E, Bettendorf O, Rody A, Jackisch C, Herschenroder F, Bocker W, & Pfleiderer B (2003) Influence of local complications on capsule formation around model implants in a rat model. J Biomed Mater Res, **64**:12-19.

Emery P & Panayi GS (1989) Autoimmune reactions to D-penicillamine. In: Kammuller ME, Bloksma N, & Seinen W eds. Autoimmunity and toxicology: Immune disregulation induced bydrugs and chemicals, pp 167-182.

Emslie-Smith AM, Engel A, Duffy J, & Bowles CA (1991) Eosinophilia Myalgia syndrome: I. Immunocytochemical evidence for a T-cell mediated immune effector response. Ann Neurol, **29**: 524-528.

Eneström S & Hultman P (1995) Does amalgam affect the immune system? A controversial issue. Int Arch Allergy Immunol, **106**: 180-203.

Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, & Brooks P (2000) Male systemic sclerosis and occupational silica exposure - a population-based study. Aust NZ J Med, **30**: 215-220.

Ennis M et al. (1990) Histamine release and pseudoallergic reactions induced by radiographic contrast media: comparison of Angiographin, Hexabrix and Telebrix using an *in vivo* canine model. Agents Actions, **30**(1-2): 81-84.

Enzer I, Dunn G, Jacobsson L, Bennett PH, Knowler WC, & Silman A (2002) An epidemiologic study of trends in prevalence of rheumotoid factor for seropositivity in Pima Indians. Arthritis Rheum, **46**: 1729-1734.

Erlandsson MC, Ohlsson C, Gustafsson JA, & Carlsten H (2001) Role of oestrogen receptors alpha and beta in immune organ development and in oestrogen-mediated effects on thymus. Immunol, **103**: 17-25.

Etzioni A (2003) Immune deficiency and autoimmunity. Autoimmunity Rev, **2**: 364-369.

Evans HL, Taioli E, Toniolo P, & El-Fawal HAN (1994) Serum autoantibody to nervous proteins: Isotypes in workers exposed to cadmium and nickel. Toxicologist, **14**: 291.

Everson MP & Blackburn WD Jr (1997) Antipolymer antibodies, silicone breast implants, and fibromyalgia [letter]. Lancet, **349**: 1171.

Evron E, Brautbar C, Becker S, Fenakel G, Abend Y, Sthoeger Z & et al (1995) Correlation between gold-induced enterocolitis and the presence of the HLA-DRB1* 0404 allele. Arthritis Rheum, **38**: 755-759.

Ezendam J (2004) Mechanisms of hexachlorobenzene-induced adverse immune effects. The Netherlands, Utrecht University (Thesis).

Ezendam J, Vissers I, Bleumink R, Vos JG, & Pieters R (2003) Immunomodulatory effects of tetrachlorobenzoquinone, a reactive metabolite of hexachlorobenzene. Chem Res Toxicol, **16**: 688-694.

Ezendam J, Hassing I, Bleumink R, Vos JG, & Pieters R (2004a) Hexachlorobenzene-induced immunopathology in Brown Norway Rats is partly mediated by T cells. Toxicol Sci, **78**: 88-95.

Ezendam J, Staedtler F, Pennings J, Vandebriel RJ, Pieters R, Harleman JH, & Vos JG (2004b) Toxicogenomics of subchronic hexachlorobenzene exposure in Brown Norway rats. Environ Health Perspect, **112**(7): 782-791.

Fagius J et al. (1985) Guillain-Barre syndrome following zimeldine treatment. J Neurol Neurosurg Psychiatry, **48**(1): 65-69.

Fairweather D, Kaya Z, Shellam GR, Lawson CM, & Rose NR (2001) From infection to autoimmunity. J Autoimmunol, **16**: 175-186.

Fan F, Pinson DM & Rozman KK (1995) Immunomodulatory effect of 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin tested by the popliteal lymph node assay. Toxicol Pathol, **23**: 513-517.
Farrell RJ & Kelly CP (2002) Celiac sprue. N Engl J Med, **346**: 180-188.

Farrell RJ & Peppercorn MA (2002) Ulcerative colitis. Lancet, **359**: 331-340.

Feld JJ & Heathcote EJ (2003) Epidemiology of autoimmune liver disease. J Gastroenterol Hepatol, **18**(10): 1118-1128.

Fellermann K, Wehkamp J, Herrlinger KR, & Stange EF (2003) Crohn's disease: a defensin deficiency syndrome? Eur J Gastroenterol Hepatol, **15**: 627-634.

Ferguson JH (1997) Silicone breast implants and neurologic disorders. Report of the Practice Committee of the American Academy of Neurology. Neurology: **48**: 1504-1507.

Ferreiros-Vidal I, Gomez-Reino JJ, Barros F, Carracedo A, Carreira P, Gonzalez-Escribano F, Liz M, Martin J, Ordi J, Vicario JL, & Gonzalez A (2004) Association of PDCD1 with susceptibility to systemic lupus erythematosus: Evidence of population-specific effects. Arthritis Rheum, **50**: 2590-2597.

Field T & Bridges AJ (1996) Clinical and laboratory features of patients with scleroderma and silicone implants. Curr Top Microbiol Immunol, **210**: 283-290.

Field AC et al. (2000) Neonatal induction of tolerance to T(h)2-mediated autoimmunity in rats. Int Immunol, **12**(10): 1467-1477.

Field AC et al. (2003) Regulatory CD8+ T cells control neonatal tolerance to a Th2-mediated autoimmunity. J Immunol, **170**(5): 2508-2515.

Fife MS, Fisher SA, John S, Worthington J, Shah CJ, Ollier WER, Panayi GS, Lewis CM, & Lanchbury JS (2000) Multipoint linkage analysis of a candidate gene locus in rheumatoid arthritis demonstrate significant evidence of linkage and association with the corticotropin-releasing hormone genomic region. Arthritis Rheum, **43**: 1673-1678.

Filaci G & Suciu-Foca N (2002) CD8+ T suppressor cells are back to the game: are they players in autoimmunity? Autoimmunity Rev, **1**: 279-283.

Firestein GS (2003) Evolving concepts of rheumatoid arthritis. Nature (Lond), **423**: 356-361.

Firestein GS, Echeverri F, Yeo M, Zvaifler NJ, Green DR. (1997) Somatic mutations in the p53 tumor suppressor gene in rheumatoid arthritis synovium. Proc Natl Acad Sci (USA), **94**: 10895-10900.

Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Leonardo MJ, & Puck JM (1995) Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell, **81**: 935-946.

Flassbeck D, Pfleiderer B, Klemens P, Heumann KG, Eltze E, & Hirner AV (2003) Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants Anal Bioanal Chem, **375**: 356-362.

Flescher E & Talal N (1991) Do viruses contribute to the development of Sjögren´s syndrom? Am J Med, **90**: 283-285.

Flockhart DA, Clauw DJ, Buchert Sale E, Hewett J, & Woosley R (1994) Pharmacogenetic characteristics of the Eosinophilia-Myalgia syndrome. Clin Pharmacol Ther, **56**: 398-405.

Folwaczny C, Glas J, & Török HP (2003) Crohn's disease: an immunodeficiency? Eur J Gastroenterol Hepatol, **15**: 621-626.

Ford CD, Johnson GH, & Smith WG (1983) Natural killer cells in *in utero* diethylstilbestrol-exposed patients. Gynecol Oncol, **16**: 400-404.

Forsberg JG (2000) Neonatal estrogen treatment and its consequences for thymus development, serum level of autoantibodies to cardiolipin, and the delayed-type hypersensitivity response. J Toxicol Environ Health A, **60**: 185-213.

Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, & Sperling RI (1995) Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. J Clin Epidemiol, **48**: 1379-1390.

Fox RI, Luppi M, Pisa P, & Kang HL (1992) Potential role of Epstein-Barr virus in Sjögren´s syndrome and rheumatoid arthritis. J Rheumatol, **19**: 18-24.

Fraser PA, Ding WZ, Mohseni M, Treadwell EL, Dooley MA, St Clair EW, Gilkeson GS, & Cooper GS (2003) Glutathion S-transferase M null homozygosity and risk of systemic lupus erythematosus associated with sun exposure: a possible gene-environmental interaction for autoimmunity. J Rheumatol, **30**: 276-282.

Frenkel K, Karkoszka J, Cohen B, Baranski B, Jakubowski M, Cosma G, Taioli E, & Toniolo P (1994) Occupational exposures to Cd, Ni, and Cr modulate titers of antioxidized DNA base autoantibodies. Environ Health Perspect, **102**(Suppl 3): 221-229.

Friedetzky A, Grau V, Wieckenberg M, Lewen A, Gemsa D, Garn H. Long term iNOS expression in thoracic lymph nodes of silicotic rats. Immunobiology. 2002 Jul;205(3):219-30.

Friedman SL. (1999) Stellate cell activation in alcoholic fibrosis--an overview. Alcohol Clin Exp Res. 23(5):904-10.

Friis S, Mellemkjaer L, McLaughlin JK, McLaughlin JK, Breiting V, Krüger Kjaer S, Blot W, & Olson JH (1997) Connective tissue disease and other rheumatic conditions following breast implants in Denmark. Ann Plast Surg, **39**: 1-8.

Fritzler MJ, Pauls JD, Kinsella TD, & Bowen TJ (1985) Antinuclear, anticytoplasmic, and anti-Sjogren's syndrome antigen A (SS-A/Ro) antibodies in female blood donors. Clin Immunol Immunopathol, **36**: 120-128.

Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, & Cantorna MT (2003) A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Mol Endocrinol, **17**: 2386-2392.

Fronczak CM, Baron AE, Chase HP, Ross C, Brady HL, Hoffman M, Eisenbarth GS, Rewers M, & Norris JM (2003) *In utero* dietary exposures and risk of islet autoimmunity in children. Diabetes Care, **26**: 3237-3242.

Fu X, Tian H, Hsu S, Wang D, & Sheng Z (1996) *In vivo* effects of tumor necrosis factor alpha on incised wound and gunshot wound healing. J Trauma, **40**(Suppl): S140-S143.

Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, & Melton LJ (1994) Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med, **330**: 1697-1702.

Garn H, Friedetzky A, Kirchner A, Jager R, Gemsa D. Experimental silicosis: a shift to a preferential IFN-gamma-based Th1 response in thoracic lymph nodes. Am J Physiol Lung Cell Mol Physiol. 2000 Jun;278(6):L1221-30.

Gadoth N (2003) Multiple sclerosis in children. Brain Dev, **25**(4): 229-232.

Gallardo S, del Pozo V, Cardaba B, de Andres B, Martin-Orozco E, Fernandez JC, Tramon P, Posada de la Paz M., Abaitua Borda I, Palomino P, and Lahoz,C. (1994) Immunological basis of Toxic oil syndrome (TOS). Toxicology, **93**: 289-299.

Gallardo S, Cardaba B, del Poza V, Belen DA, Cortegano MI, Jurado A, Tramon P, Palomino P, & Lahoz C (1997) Study of apoptosis in human lymphocytes by toxic substances implicated in Toxic oil syndrome. Toxicology, **118**: 71-82.

Garabrant DH & Dumas C (2000) Epidemiology of organic solvents and connective tissue disease. Arthrtis Res, **2**: 5-15.

Garchon HJ (2003) Genetics of autoimmune myasthenia gravis, a model for antibody-mediated autoimmunity in man. J Autoimmun, **21**: 105-110.

Gaubitz M, Jackisch C, Domschke W, Heindel W, & Pfleiderer B (2002) Silicone breast implants: correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. Rheumatology, **41**: 129-135.

Gehrs BC & Friedberg RC (2002) Autoimmune hemolytic anemia. Am J Hematol, **69**: 258-271.

Geier MR & Geier DA (2003) Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. Exp Biol Med, **228:** 660-664.

Gelpi E, Posada de la Paz M, Terracini B, Abaitua I, Gomez de la Camara A, Kilbourne EM, Lahoz C, Nemery B, Philen RM, Soldevilla L, & Tarkowski S (2002) The Spanish Toxic oil syndrome 20 years after its onset: A multidisciplinary review of scientific knowledge. Environ Health Perspect, **110**: 457-464.

Gell PGH and Coombs RRA, Eds. (1963) Clinical Aspects of Immunology. FA Davis Company, Philadelphia, PA publishers.

Gerszten PC (1999) A formal risk assessment of silicone breast implants. Biomaterials, **20**: 1063-1069.

Ghio AJ, Kennedy TP, Schapira RM, Crumbliss AL, & Hoisal JR (1990) Hypothesis: is lung disease after silicate inhalation caused by oxidant generation? Lancet, **336**: 967-969.

Ghosh S, Shand A, & Ferguson A (2000) Ulcerative colitis. Brit Med J, **320**: 1119-1123.

Giacomelli R, Matucci-Cerinic M, & Bombardieri S (2002) Microchimerism in Sjögren's syndrome. Ann Rheum Dis, **61**: 1039-1040.

Gilbert KM, Whitlow AB, & Pumford NR (2004) Environmental contaminant and disinfection by-product trichloroacetaldehyde stimulates T cells *in vitro*. Int Immunopharmacol, **4**: 25-36.

Gleichmann H (1981) Studies on the mechanism of drug sensitization: T-cell-dependent popliteal lymph node reaction to diphenylhydantoin. Clin Immunol Immunopathol, **18**(2): 203-211.

Gocmen A, Peters HA, Cripps DJ, Morris CR, & Dogramaci I (1986) Porphyria turcica: hexachlorobenzene-induced porphyria. In: Morris C & Cabral JR, eds Hexachlorobenzene: Proceedings of an international symposium. Lyon, France, International Agency for Research on Cancer, pp 567-573 (IARC Scientific Publications No. 77).

Goebel C et al. (1996) The popliteal lymph node assay in mice: screening of drugs and other chemicals for immunotoxic hazard. Inflamm Res, **45**(Suppl 2): S85-S90.

Goebel C et al. (1999) Procainamide, a drug causing lupus, induces prostaglandin H synthase-2 and formation of T cell-sensitizing drug metabolites in mouse macrophages. Chem Res Toxicol, **12**(6): 488-500.

Goldblum RM, Pelley RP, O'Donell AA, Pyron D, & Heggers JP (1992) Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. Lancet, **340**: 510-513.

Goldblum RM, Pyron D, & Shenoy M (1995) Modulation of IgG binding to silicone by human serum. FASEB J, **9**: A1029.

Golden RJ, Noller KL, Titus-Ernstoff L, Kaufman RH, Mittendorf R, Stillman R, & Reese EA (1998) Environmental endocrine modulators and human health: an assessment of the biological evidence. Crit Rev Toxicol, **28**: 109-227.

Gomez de la Camara A, Abaitua Borda I, & Posada de la Paz M (1997) Toxicologists versus toxicological disasters: Toxic oil syndrome, clinical aspects. Berlin, Heidelberg, Springer Verlag.

González S, Martínez-Borra J, López-Vásquez A, García-Fernández S, Torre-Alonso JC, & López-Larrea C (2002) MICA rather than MICB, TNFA, or HLA-DRB1 is associated with susceptibility to psoriatic arthritis. J Rheumatol, **29**: 973-978.

González-Escribano NF, Morales J, García-Lozano JR, Castillo MJ, Sánchez-Roman J, Núnez-Roldán A, & Sanchez B (1995) TAP polymorphism in patients with Behcet's disease. Ann Rheum Dis, **54**: 386-388.

Gonzalez-Escribano MF, Rodriguez R, Valenzuela A, Garcia A, Garcia-Lozano JR, & Nunez-Roldan A (1999) CTLA4 polymorphisms in Spanish patients with rheumatoid arthritis. Tissue Antigens, **53**: 296–300.

Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, & Llorca J (2003) The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. Arthritis Rheum, **49**(3): 388-393.

Goodin DS (2004) Relationship between multiple sclerosis exacerbations and stress. Psychosomatic Med, **66**: 287-289.

Gorrie MJ, Qasim FJ, Whittle CJ *et al* (2000) Exogenous type-1 cytokines modulate mercury-induced hyper-IgE in the rat. Clin Exp Immunol, **121**: 17-22.

Goter-Robinson CJ, Balasz T, & Egorov IK (1986) Mercuric chloride, gold sodium thiomalate, and D-penicillamine induced antinuclear antibodies in mice. Toxicol Appl Pharmacol, **86**: 159-169.

Goverman J (1999) Tolerance and autoimmunity in TCR transgenic mice specific for myelin basic protein. Immunol Rev, **169**: 147-159.

Graham RR, Ortmann WA, Langefeld CD, Jawaheer D, Selby SA, Rodine PR, Baechler EC, Rohlf KE, Shark KB, Espe KJ, Green LE, Nair RP, Stuart PE, Elder JT, King RA, Moser KL, Gaffney PM, Bugawan TL, Erlich HA, Rich SS, Gregersen PK, Behrens TW. (2002) Visualizing human leukocyte antigen class II risk haplotypes in human systemic lupus erythematosus. Am J Hum Genet, **71**: 543-553.
Gran JT, Husby G, & Thorsby E (1983) HLA-DR antigens and gold toxicity. Ann Rheum Dis, **41**: 63-71.

Granum B, Gardner PI, Groeng E, Leikvold R, Namork E, & Lovik M (2001) Fine particles of widely different composition have an adjuvant effect on the production of allergen-specific antibodies. Toxicol Lett, **118**: 171-181.

Greenberg GN & Dement JM (1994) Exposure assessment and gender differences. J Occup Environ Med, **36**: 907-912.

Greene WB, Raso DS, Walsh LG, HArley RA, & Silver RM (1995a) Electron probe microanalysis of silicon and the role of the macrophage in proximal (capsule) and distant sites in augmentation mammoplasty patients. Plast Reconstr Surg, **95**: 513-519.

Greene WB, Raso DS, Willingham MC, Greene AS, & Makeef JA (1995b) Migration of silicone gel from breast implants. Eur Microscop Analysis, **May**: 31-33.

Greenfield EA, Nguyen KA, & Kuchroo VK (1998) CD28/B7 co-stimulation: a review. Crit Ver Immunol, **18**: 389-418.

Gregersen PK, Silver J, & Winchester RJ (1987) The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum, **30**: 1205-1213.

Gregorini G, Ferioli A, Donato F, Tira P, Morassi L, Tardanico R, Lancini L, & Maiorca R (1993) Association between silica exposure and necrotizing crescentic glomerulonephritis with p-ANCA and anti-MPO antibodies: a hospital- based case-control study. Adv Exp Med Biol, **336**: 435-440.

Gregorini G, Tira P, Frizza J, D'Haese PC, Elseviers MM, Nuyts G, Maiorca R, & De Broe ME (1997) ANCA-associated diseases and silica exposure. Clin Rev Allergy Immunol, **15**: 21-40.

Griem P, Wulferink M, Sachs B, González JB, & Gleichmann E (1998) Allergic and autoimmune reactions to xenobiotics: how do they arise? Immunol Today, **19**: 133-141.

Griffin JM, Gilbert KM, Lamps LW, & Pumford NR (2000a) CD4(+) T-cell activation and induction of autoimmune hepatitis following trichloroethylene treatment in MRL +/+ mice. Toxicol Sci, **57**: 345-352.

Griffin JM, Gilbert KM, & Pumford NR (2000b) Inhibition of CYP2E1 reverses CD4+ T-cell Alterations in Trichloroethylene-treated MRL+/+ Mice. Toxicol Sci, **54**: 384-389.

Grodzicky T & Elkon KB (2002) Apoptosis: A case where too much or too little can lead to autoimmunity. Mt Sinai J Med, **69**: 208-219.

Grove J, Brown AS, Daly AK, Bassendine MF, James OF, Day CP. (1998) The RsaI polymorphism of CYP2E1 and susceptibility to alcoholic liver disease in Caucasians: effect on age of presentation and dependence on alcohol dehydrogenase genotype. Pharmacogenetics. 8(4):335-42.

Grove J, Daly AK, Bassendine MF, & Day CP (1997) Association of a tumor necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitus. Hepatology, **26**: 143-146.

Grove J, Daly AK, Bassendine MF, Gilvarry E, & Day CP (2000) Interleukin 10 promoter region polymorphisms and susceptibility to advanced alcoholic liver disease. Gut, **46**: 540-545.

Guo XM & Rhodes J (1990) An essential role for constitutive Schiff base-forming ligands in antigen presentation to murine T cell clones. J Immunol, **144**: 2883-2890.

Gutierrez MA, Garcia ME, Rodriguez JA, Rivero S, & Jacobelli S (1998) Hypothalamic-pituitary-adrenal axis function and prolactin secretion in systemic lupus erythematosus. Lupus, **7**: 404-408.

Gutting BW et al. (1999) A comparison of the direct and reporter antigen popliteal lymph node assay for the detection of immunomodulation by low molecular weight compounds. Toxicol Sci, **51**(1): 71-79.

Gutting BW, Updyke LW, & Amacher DE (2002a) Investigating the TNP-OVA and direct popliteal lymph node assays for the detection of immunostimulation by drugs associated with anaphylaxis in humans. J Appl Toxicol, **22**(3): 177-183.

Gutting BW, Updyke LW, & Amacher DE (2002b) BALB/c mice orally pretreated with diclofenac have augmented and accelerated PLNA responses to diclofenac. Toxicology, **172**(3): 217-230.

Hajeer AH, Worthington J, Silman AJ, & Ollier WER (1996) Association of tumor necrosis factor microsatellite polymorphisms with HLA-DRB1*04-bearing haplotypes in rheumatoid arthritis patients. Arthritis Rheum, **39**: 1109-1114.

Hakala M, Silvennoinen-Kassinen S, Ikäheimo I, Isosomppi J, & Tilikainen A (1997) HLA markers in a community based rheumatoid arthritis series. Ann Med, **29**: 291-296.

Hall GM, Daniels M, Huskisson EC, & Spector TD (1994) A randomized controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. Ann Rheum Dis, **53**: 112-116.

Hall A, Kane M, Roure C, & Mehus (1999) Multiple sclerosis and hepatitis B vaccine? Vaccine, **17**: 2473-2475.

Hall AJ, Yee LJ, & Thomas SL (2002) Life course epidemiology and infectious diseases. Int J Epidemiol, **31**(2): 300-301.

Hammarstrom L, Lerckovsky I, & Webster DB (2000) Selective IgA deficiency and common variable immunodeficiency. Clin Exp Immunol, **120**: 225.

Han Z, Boyle DL, Shi Y, Green DR, & Firestein GS (1999) Dominant-negative p53 mutations in rheumatoid arthritis. Arthritis Rheum, **42**: 1088-1092.

Hanley GA, Schiffenbauer J, & Sobel ES (1998) Resistance to $HgCl_2$-induced autoimmunity in haplotype-heterozygous mice is an intrinsic property of B cells. J Immunol, **161**: 1778-1785.

Hard GC (2000) Short-term adverse effects in humans of ingested mineral oils, their additives, and possible contaminants -- A review. Hum Exp Toxicol, **19**: 158-172.

Hard GC (2002) A search for an animal model of the Spanish Toxic oil syndrome. Food Chem Toxicol, **40**: 1551-1567.

Hari CK, Raza SA, & Clayton MI (1998) Hydralazine-induced lupus and vocal fold paralysis. J Laryngol Otol, **112**(9): 875-877.

Harness J & McCombe PA (2001) The effects of pregnancy on myelin basic protein-induced experimental autoimmune encephalomyelitis in Lewis rats: Suppression of clinical disease, modulation of cytokine expression in the spinal cord inflammatory infiltrate and suppression of lymphocyte proliferation by pregnancy sera. Am J Reprod Immunol, **46**: 405-412.

Harness J, Cavanagh A, Morton H, & McCombe P (2003) A protective effect of early pregnancy factor on experimental autoimmune encephalomyelitis induced in Lewis rats by inoculation with myelin basic protein. J Neurol Sci, **216**: 33-41.

Harrison BJ (2002) Influence of cigarette smoking on disease outcome in rheumatoid arthritis. Curr Opin Rheumatol, **14**: 93-97.

Hastings KL (2001) Pre-clinical methods for detecting the hypersensitivity potential of pharmaceuticals: regulatory considerations. Toxicology, **158**(1-2): 85-89.

Haustein UF & Ziegler V (1985) Environmentally induced systemic sclerosis-like disorders. Int J Dermatol, **24**: 147-151.

Havarinasab S, Lambertsson L, Qvarnstrom J, & Hultman P (2004) Dose-response study of thimerosal induced murine systemic autoimmunity. Toxicol Appl Pharmacol, **194:** 169-179.

Hawkins BR, Dawkins RL, Burger HG, MacKay IR, Cheah PS, Whittingham S, Patel Y, & Welborn TA (1980) Diagnostic significance of thyroid microsomal antibodies in randomly selection population. Lancet, **2**: 1057-1059.

Heldt C, Listing J, Sözeri O, Bläsing F, Frishbutter S, & Müller B (2003) Differential expression of HLA class II genes associated with disease susceptibility and progression in rheumatoid arthritis. Arthritis Rheum, **48**: 2779-2787.

Heliovaara M, Aho K, Knekt P, Impivaara O, Reunanen A, & Aromaa A (2000) Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. Ann Rheum Dis, **59**: 631-635.

Henly DR, Barratt DM, Weiland TL, OÇonnor MK, Malizia AA, & Wein AJ (1995) Particulate silicone for use in periurethral injections: local tissue effects and search for migration. J Urology, **153**: 2039-2043.

Hennekens CH, Lee IM, Cook NR, Hebert PR, Karlson EW, LaMotte F, Manson JE, & Buring JE (1996) Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. J Am Med Assoc, **275**: 616-621.

Hertzman PA, Blevins WL, Mayer J, Greenfield B, Ting M, & Gleich GJ (1990) Association of the Eosinophilia-Myalgia syndrome with the ingestion of tryptophan. N Engl J Med, **322**: 869-873.

Hertzman PA, Clauw DJ, Kaufman LD, Varga J, Silver RM, Thacker HL, Mease P, Espinoza LR, & Pincus T (1995) The Eosinophilia Myalgia syndrome: Status of 205 patients and results of treatment two years after onset. Ann Intern Med, **122**: 851-855.

Hernan MA, Hohol MJ, Olek MJ, Spiegelman D, & Ascherio A (2000) Oral contraceptives and the incidence of multiple sclerosis. Neurology, **55**: 848-854.

Hernan MA, Oleky MJ, & Ascherio A (2001) Cigarette smoking and incidence of multiple sclerosis. Am J Epidemiol, **154**: 69-74.

Herold KC et al. (1996) Regulation of cytokine production during development of autoimmune diabetes induced with multiple low doses of streptozotocin. J Immunol, **156**(9): 3521-3527.

Hill RH, Caudill SP, Philen RM, Bailey SL, Flanders WD, Driskell WJ, Kamb ML, Needham LL, & Sampson EJ (1993) Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. Arch Environ Contam Toxicol, **25**: 134-142.

Hill RH Jr, Schurz HH, Posada de la Paz M, Abaitua Borda I, Philen RM, Kilbourne EM, Head SL, Bailey SL, DriskellWJ, and Barr JR. (1995) Possible etiologic agents for Toxic oil syndrome: Fatty acid esters of 3-(N-phenylamino)-1,2-propanediol. Arch Environ Contam Toxicol, **28**: 259-264.

Hill SL, Landavere MG, & Rose NR (1996) The adjuvant effect of silicone gel and silicone elastomer particles in rats. Curr Top Microbiol Immunol, **210**: 123-37.

Hirsch F et al. (1982) Polyclonal effect of HgCl2 in the rat, its possible role in an experimental autoimmune disease. Eur J Immunol, **12**(7): 620-625.

Hirsch F et al. (1986) Autoimmunity induced by HgCl2 in Brown-Norway rats. I. Production of monoclonal antibodies. J Immunol, **136**(9): 3272-3276.

Hitraya EG, Jimenez SA, Ludwicka A, Silver RM, & Varga J (1997) Increased activity of the a1(I) procollagen promoter in skin fibroblasts from patients with chronic eosinophilia-myalgia syndrome. Int J Biochem Cell Biol, **29**: 135-141.

Hochberg MC & Perlmutter DL (1996) The association of augmentation mammoplasty with connective tissue disease, including systematic sclerosis (scleroderma): a meta-analysis. Curr Top Microbiol Immunol, **210**: 411-417.

Hochberg MC & Petri M (1993) Clinical features of systemic lupus erythematosus. Curr Opin Rheumatol, **5**: 575-586.

Hochberg MC, Perlmutter DL, Medsger TA Jr, Nguyen K, Steen V, Weisman MH, White B, & Wigley FM (1996) Lack of association between augmentation mammoplasty and systemic sclerosis (scleroderma). Arthritis Rheum, **39**: 1125-1131.

Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, Blom B, Homola ME, Streit WJ, Brown MH, Barclay AN, Sedgwick JD. (2000) Downregulation of the macrophage lineage through interaction with OX2 (CD200). Science, **290**: 1768-1771.

Hoffman RA, Stehr-Green PA, Webb KB, Evans RG, Knussen AP, Schramm WF, Staake JL, Gibson BB, & Steinberg KK (1986) Health effects of long-term exposure to 2,3,7,8-tetra-chlorodibenzo-*p*- dioxin. J Am Med Assoc, **255**: 2031-2038.

Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, & Falk RJ (2001) Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. J Am Soc Nephrol, **12**: 134-142

Holladay SD (1999) Prenatal immunotoxicant exposure and postnatal autoimmune disease. Environ Health Perspect, **107**(Suppl 5): 687-691.

Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, & Braverman LE (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab, **87**: 489-499.

Holmdahl R et al. (1999) Transgenic mouse models of rheumatoid arthritis. Immunol Rev, **169**: 161-173.

Holmich LR, Friis S, Fryzek JP, Vejborg IM, Conrad C, Sletting S, Kjoller K, McLaughlin JK, & Olsen JH (2003a) Incidence of silicone breast implant rupture. Arch Surg, **138**: 801-806.

Holmich LR, Kjoller K, Fryzek JP, Hoier-Madsen M, vejborg I, Conrad C, Sletting S, McLaughlin JK, Breiting V, & Friis S (2003b) Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. Plast Reconstr Surg, **111**: 723-732.

Hopkinson ND, Doherty M, & Powell RJ (1993) The prevalence and incidence of systemic lupus erythematosus in Nottingham, UK, 1989-1990. Br J Rheumatol, **32**: 110-115.

Horiuchi T, Nishizaka H, Yasunaga S, Higuchi M, Tsukamoto H, Hayashi H, & Nagasawa K (1999) Association of Fas/Apo-1 gene polymorphism with systemic lupus erythematosus in Japanese. Rheumatol, **38**: 516-520.

Horseman ND & Yu-Lee LY (1994) Transcriptional regulation by the helix bundle peptide hormones: growth hormone, prolactin, and hematopoietic cytokines. Endocrinol Rev, **15**: 627-649.

Hrubec Z & Omenn GS (1981) Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological end points by zygosity among male veterans. Alcohol Clin Exp Res, **5**: 207-215.

Huang SH, Hubbs AF, Stanley CF, Vallyathan V, Schnabel PC, Rojanasakul Y, Ma JK, Banks DE, & Weissman DN (2001) Immunoglobulin responses to experimental silicosis. Toxicol Sci, **59**: 108-117.

Hudson CA, Cao L, Kasten-Jolly J, Kirkwood JN, & Lawrence DA (2003) Susceptibility of lupus-prone NZM mouse strains to lead exacerbation of systemic lupus erythematosus symptoms. J Toxicol Environ Health, **A23**: 895-918.

Huizinga TW, van der Linder MW, Deneys-Laporte V, & Breedveld FC (1999) Interleukin-10 as an explanation for pregnancy-induced flare in systemic lupus erythematosus. Rheumatology, **38**: 496-498.

Hultman P & Enestrom S (1992) Dose-response studies in murine mercury-induced autoimmunity and immune-complex disease. Toxicol Appl Pharmacol, **113**(2): 199-208.

Hultman P & Nielsen JB (2001) The effect of dose, gender, and non-H-2 genes in murine mercury-induced autoimmunity. J Autoimmun, **17**: 27-37.

Hultman P, Johansson, Turley SJ, Lindh U, Enestrom S, & Pollard KM (1994) Adverse immunological effects and autoimmunity induced by dental amalgam and alloy in mice. FASEB J, **8**: 1183-1190.

Hultman P, Turkey SJ, Enestrom S, Lindh U, & Pollard KM (1996) Murine genotype influences the specificify, magnitude and persistence of murine mercury-induced autoimmunity. J Autoimmun, **9**: 139.

Hunter I, Greene SA, MacDonald TM, & Morris AD (2000) Prevalence and aetiology of hypothyroidism in the young. Arch Dis Child, **83**(3): 207-210.

Hunziker H (1978) Gold induced autoimmunohemolytic anemia. Praxis, **67**: 702-704.

Hurtenbach U et al. (1987) Immunity to D-penicillamine: genetic, cellular, and chemical requirements for induction of popliteal lymph node enlargement in the mouse. J Immunol, **139**(2): 411-416.

Hviid A, Stellfield M, Wolfahrt J, & Melbye M (2004) Childhood vaccination and type 1 diabetes. N Engl J Med, **350**: 1398-1404.

Hypponen E (2004) Micronutrients and the risk of type 1 diabetes: vitamin D, vitamin E, and nicotinamide. Nutr Rev, **62**: 340-347.

Iribarren P, Correa SG, Sodere N, & Riera CM (2002) Activation of macrophages by silicones: phenotype and production of oxidant metabolites. BMC Immunol, **3**: 6.

IPCS (1996) Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 180).

IPCS (1999) Principles and methods for assessing allergic hypersensitization associated with exposure to chemicals. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 212).

Imai S, Tezuka H, & Fujita K (2001) A factor of inducing IgE from a filarial parasite prevents insulin-dependent diabetes mellitus in nonobese diabetic mice. Biochem Biophys Res Commun, **286**(5): 1051-1058.

Izumi Y, Tanaka S, Hidaka Y, Shimaoka Y, Tatsumi KI, Takano T, Kaneko A, Oku K, & Amino N (2003) Relation between post-partum liver dysfunction and anti-cytochrome 2D6 antibodies. Am J Reprod Immunol, **50**: 355-362.

Iyer R, Hamilton RE, Li L, & Holian A (1996) Silica-induced apoptosis mediated via scavenger receptor in human alveolar macrophages. Toxicol Appl Pharmacol, **141**: 84-92.

Jacobson DL, Gange SJ, Rose NR, & Graham NM (1997) Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol, **84**(3): 223-243.

Janowski EC, Kupper LL, & Hulka BS (2000) Meta-analysis of the relation between silicone breast implants and the risk of connective tissue diseases N Engl J Med, **342**: 781-790.

Jarvelainen HA, Orpana A, Perola M, Savolainen VT, Karhunen PJ, & Lindros KO (2001) Promoter polymorphism of the CD14 endotoxin receptor gene as a risk factor for alcoholic liver disease. Hepatology, **33**: 1148-1153.

Jennings AM, Wild G, Ward JD, & Ward AM (1988) Immunological abnormalities 17 years after accidental exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Br J Ind Med, **45**: 701-704.

Jensen B, Wiik A, Hewchmann Wittrup I, Friis S, Shen GQ, Bliddal H, McLaughlin JK, Lykke Thomson B, Dannekiold-Samsoe B, & Olsen JH (2003) Silicate antibodies in Danish women with silicone breast implants. Rheumatology, **42**:1032-1035.

Jensen B, Wittrup IH, Wiik A, Bliddal H, Friis AS, McLaughlin JK, Danneskiold-Samsoe B, & Olsen JH (2004) Antipolymer antibodies in Danish fibromyalgia patients. Clin Exp Rheumatol, **22**: 227-229.

Jimenez SA & Artlett CM (2005) Microchimerism and systemic sclerosis. Curr Opin Rheumatol, **17**: 86-90.

Johnson AE, Gordon C, Palmer RG, & Bacon PA (1995) The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum, **38**: 551-558.

Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, & Moustsopoulos HM (1998) Hypofunction of the stress axis in Sjogren's syndrome. J Rheumatol, **25**: 1508-1514.

Jonsson TH, Thorsteinsson J, & Valdimarsson H (1998) Does smoking stimulate rheumatoid factor production in nonrheumatic individuals? APMIS, **106**: 970-974.

Jonsson R, Haga HJ, & Gordon TP (2000) Current concepts on diagnosis, autoantibodies and therapy in Sjogren's syndrome. Scand J Rheumatol, **29**: 341-348.

Joshi BG, Dwivedi C, Powell A, & Holscher M (1981) Immune complex nephritis in rats induced by long-term oral exposure to cadmium. J Comp Pathol, **91**: 11-15.

Jung D, Berg PA, Edler L, Ehrenthal W, Fenner D, Flesch-Janys D, Huber C, Klein R, Koitka C, Lucier G, Manz A, Muttray A, Needham L, Päpke O, Pietsch M, Portier C, Patterson D, Prellwitz W, Rose DM, Thews A, & Konietzko J (1998) Immunological findings in workers formerly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and its congeners. Environ Health Perspect, **106**(Suppl 2): 689-695.

Kala SV, Lykissa ED, Neely MW, & Lieberman MW (1998) Low molecular weight silicones are widely distributed after a single subcutaneous injection in mice. Am J Pathol, **152**: 645-649.

Kalb B, Matell G, Pirskanen R, & Lambe M (2002) Epidemiology of myasthenia gravis: a population-based study in Stockholm, Sweden. Neuroepidemiology, **21**: 221-225.

Kamb ML, Murphy JJ, Jones JL, Caston JC, Nederlof K, Horney LF, Swygert LA, Falk H, & Kilbourne EM (1992) Eosinophilia-malgia syndrome in L-tryptophan-exposed patients. J Am Med Assoc, **267**: 77-82.

Kamel M, Protzner K, Fornassier V, Peters W, Smith D, & Ibanez D (2001) The peri-implant breast capsule: an immunophenotypic study of capsules taken at explantation surgery. J Biomed Mater Res, **58**: 88-96.

Kammuller ME & Seinen W (1988) Structural requirements for hydantoins and 2-thiohydantoins to induce lymphoproliferative popliteal lymph node reactions in the mouse. Int J Immunopharmacol, **10**(8): 997-1010.

Kammuller ME, Bloksma N, & Seinen W (1988) Chemical-induced autoimmune reactions and Spanish Toxic oil syndrome: Focus on hydantions and related compounds. Clin Toxicol, **26**: 157-174.

Kammuller ME, Bloksma N, & Seinen S (1989a) Autoimmunity and toxicology: Immune disregulation induced by drugs and chemicals. In: Kammuller ME & Bloksma N, & Seinen W eds. Autoimmunity and toxicology immune disregulation induced by drugs and chemicals, pp. 3-34.

Kammuller ME et al. (1989b) The popliteal lymph node assay in mice to screen for the immune disregulating potential of chemicals--a preliminary study. Int J Immunopharmacol, **11**(3): 293-300.

Kanemitsu S, Ihara K, Saifddin A, Otsuka T, Takeuchi T, Nagayama J, Kuwano M, & Hara T (2002) A functional polymorphism in Fas (CD95/APO-1) gene promotor associated with systemic lupus erythematosus. J Rheumatol, **29**: 1183-1188.

Kantarci OH, Hebrink DD, Achenbach SJ, Atkinson EJ, Waliszewska A, Buckle G McMurray CT, de Andrade M, Hafler DA, Weinshenker BG. (2003) CTLA4 is associated with susceptibility to multiple sclerosis. J Neuroimmunol, **134**: 133–141.

Karlson EW, Hankinson SE, Liang MH, Sanchez-Guerrero J, Colditz GA, Rosenau BJ, Speizer FE, & Schur PH (1999) Association of silicone breast implants with immunologic abnormalities: a prospective study. Am J Med, **106**: 11-19.

Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, & Tuomilehto J (2000) Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. Diabetes Care, **78**(1) : 84-88.

Katsutani,N & Shionoya H (1992) Drug-specific immune responses induced by immunization with drugs in guinea pigs and mice. J Toxicol Sci, **17**(4): 169-183.

Kaufman L & Krupp L (1995) Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia. Curr Opin Rheum, 7: 560-567.

Kaufman LD, Gruber BL, & Gregersen PK (1991) Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. Lancet, **337**: 1071-1074.

Kaufman LD, Izquierdo Martinez M, Serrano JM, & Gomez-Reino JJ (1995a) 12-year followup study of epidemic Spanish Toxic oil syndrome. J Rheumatol, 22: 282-288.

Kaufman LD, Varga J, Gomez-Reino JJ, Jimenez S, & Targoff IN (1995b) Autoantibodies in sera from patients with L-tryptophan-associated eosinophilia-myalgia syndrome. Clin Immunol Immunopathol, **76**: 115-119.

Kerkvliet NI (1998) Review of animal studies relevant to silicone toxicity. Report of National Science Panel, Chapter 1.

Kerkvliet NI (2002) Recent advances in understanding the mechanisms of TCDD immunotoxicity. Int Immunopharm, **2**: 277-291.

Kessler DA (1992) The basis of the FDA's decision on breast implants. N Engl J Med, **326**: 1713-1715.

Khamashta MA, Ruiz-Irastorza G, & Hughes GR (1997) Systemic lupus erythematosus flares during pregnancy. Rheum Dis Clin North Am, **23**: 15-30.

Khan MF, Kaphalia BS, Prabhakar BS, Kanz MF, & Ansari GA (1995) Trichloroethene induced autoimmune response in female MRL +/+ mice. Toxicol Appl Pharmacol, **134**: 155-160.

Khan MF, Wu X, & Ansari GA (2001) Anti-malondialdehyde antibodies in MRL +/+ mice treated with trichloroethene and dichloroacetyl chloride: possible role of lipid peroxidation in autoimmunity. Toxicol Appl Pharmacol, **170**: 88-92.

Khani-Hanjani A, Lacaille D, Horne C, Chalmers A, Hoar DI, Balshaw R, & Keown PA (2002) Expression of QK/QR/RRRAA or DERAA motifs at the third hypervariable region of HLA-DRB1 and disease severity in rheumatoid arthritis. J Rheumatol, **29**:1358-1365.

Khurana R & Chauhan RS (2002) Pesticide induced immune complex mediated glomerulonephritis in sheep. J Immunol Immunopathol, **4**(1-2): 40-42.

Kilburn KH & Warshaw RH (1992) Prevalence of symptoms of systemic lupus erythematosus (SLE) and of fluorescent antinuclear antibodies assocaited with chronic exposure to trichloroethylene and other chemicals in well water. Environ Res, **57**: 1-9.

Kim HA, Kim EM, Park YC, Yu JY, Hong SK, Jeon SH, Park KL, Hur SJ, & Heo Y (2003a) Immunotoxicological effects of Agent Orange exposure to the Vietnam War Korean veterans. Ind Health, **41**: 158-166.

Kim HJ, Jeong KS, Park SJ, Cho SW, Son HY, Kim SR, Kim SH, An MY & Ryu SY (2003b) Effect of benzo[alpha]pyrene, 2-bromopropane, phenol and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on IL-6 production in mice after single or repeated exposure. In Vivo, **17**: 269-275.

Kimpimaki T, Kupila A, Hamalainen AM, Kukko M, Kulmala P, Savola K, Simell T, Keskinen P, Ilonen J, Simell O, & Knip M (2001) The first signs of beta-cell autoimmunity appear in infancy in genetically susceptible children from the general population: the Finnish Type 1 Diabetes Prediction and Prevention Study. J Clin Endocrinol Metab, **86**: 4782-4788.

Kirchner J, Stein A, Viel ,K & Jacobi V (1997) Hamman-Rich-Syndrom bei einenm Goldschmied. Aktuelle Radiol, **7**: 321-323.

Kjoller K, Friis S, Mellemkjaer L, McLaughlin JK, Winther JF, Lipworth L, Blot WJ, Fryzek J, & Olsen JH (2001) Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. Arch Intern Med, **161**: 973-979.

Kjoller K, Holmich LR, Jacobsen PH, Friis S, Fryzek J, McLaughlin JK, Lipworth L, Henriksen TF, Jorgensen S, Bittman S, & Olsen JH (2002) Epidemiological investigation of local complications after cosmetic breast implant surgery in Denmark. Ann Plast Surg, **48**: 229-237.

Klockars M, Koskela R-S, Jarvinen E, Kolari PJ, & Rossi A (1987) Silica exposure and rheumatoid arthiris: a follow-up study of granite workers 1940-81. Br Med J, **294**: 997-1000.

Klykken PC & White KL Jr (1996) The adjuvancy of silicones: dependency on compartmentalization. Curr Top Microbiol Immunol, **210**: 113-121.

Knekt P, Heliovaara M, Aho K, Alfthan G, Marniemi J, & Aromaa A (2000) Serum selenium, serum alpha-tocopherol, and the risk of rheumatoid arthritis. Epidemiology, **11**: 402-405.

Koller LD, Stang BV, Posada de la Paz M, & Ruiz-Mendez MV (2001) Pathology of "toxic oils" and selected metals in the MRL/lpr mouse. Toxicol Pathol. 2001 Nov-Dec; 29(6):630-8.

Koller LD, Stang BV, Hall JA, Posada de la Paz M, & Ruiz-Mendez MV (2002) Immunoglobulin and autoantibody responses in MRL/lpr mice treated with "toxic oils". Toxicology, **178**: 119-133.

Kono DH, Balomenos D, Park MS, & Theofilopoulos AN (2000) Development of lupus in BXSB mice is independent of IL-4. J Immunol, **164**: 38-42.

Korn JH (1997) Antipolymer antibodies, silicone breast implants, and fibromyalgia [letter]. Lancet, **349**: 1171.

Kornek B & Lassmann H (2003) Neuropathology of multiple sclerosis-new concepts. Brain Res Bull, **61**: 321-326.

Korpilähde T, Heliovaara M, Kaipiainen-Seppanen O, Knekt P, & Aho K (2003) Regional differences in Finland in the prevalence of rheumatoid factor in the presence and absence of arthritis. Ann Rheum Dis, **62**: 353-355.

Kosuda LL & Bigazzi PE (1996) Chemical-induced autoimmunity. In: Smialowicz RJ & Holsapple MP eds Experimental immunotoxicology, pp. 419-465.

Kosuda LL et al. (1994) Role of RT6+ T lymphocytes in mercury-induced renal autoimmunity: experimental manipulations of "susceptible" and "resistant" rats. J Toxicol Environ Health, **42**(3): 303-321.

Kosugi A, Sharrow SO, & Shearer GM (1989) Effect of cyclosporin A on lymphopoiesis. I. Absence of mature T cells in thymus and periphery of bone marrow transplanted mice treated with cyclosporin A. J Immunol, **142**(9): 3026-3032.

Kotsy MP, Hench PK, Tani P, & McMillan R (1989) Thrombocytopenia associated with aurofin therapy: evidence for a gold-dependent immunologic mechanism. Am J Hematol, **30**: 236-239.

Kozhevnikova G, Kuzmin I, Roumak V, & Karaulov A (1991) Immune alteration in South Vietnamese exposed to Agent Orange. In: Dioxin ’91 - Proceeding of the 11th International Symposium on Chlorinated Dioxins and Related Compounds, p.117, Research Triangle Park, North Carolina, U.S.A.

Kralovicova J, Hammarström L, Plebani A, Webster ADB, & Vorechovsky I (2003) Fine-scale mapping at IGAD1 and genome-wide genetic lingage analysis implicate HLA-DQ/DR as a major susceptibility locus in selective IgA deficiency and common variable immunodeficiency. J Imunol, **170**: 2765-2775.

Kretz-Rommel A & Rubin RL (1999) Persistence of autoreactive T cell drive is required to elicit anti-chromatin antibodies in a murine model of drug-induced lupus. J Immunol, **162**(2) : 813-820.

Kretz-Rommel A & Rubin RL (2000) Disruption of positive selection of thymocytes causes autoimmunity. Nat Med, **6**(3): 298-305.

Kretz-Rommel A & Rubin RL (2001) Early cellular events in systemic autoimmunity driven by chromatin-reactive T cell. Cell Immunol, **208**(2): 125-136.

Kretz-Rommel A, Duncan SR, & Rubin RL (1997) Autoimmunity caused by disruption of central T cell tolerance. A murine model of drug-induced lupus. J Clin Invest, **99**(8): 1888-1896.

Kristofferson A & Nilsson BS (1989) Zimeldine: febrile reactions and peripheral neuropathy. In: Kammuller ME, Bloksma N, & Seinen W eds.Autoimmunity and toxicology: Immune disregulation induced by drugs and chemicals, pp 183-214.

Kubicka-Muranyi M et al. (1995) Mercuric-chloride-induced autoimmunity in mice involves up-regulated presentation by spleen cells of altered and unaltered nucleolar self antigen. Int Arch Allergy Immunol, **108**(1): 1-10.

Kubicka-Muranyi M et al. (1996) Murine systemic autoimmune disease induced by mercuric chloride: T helper cells reacting to self proteins. Int Arch Allergy Immunol, **109**(1): 11-20.

Kühtreiber WM, Hayashi T, Dale EA, & Faustman DL (2003) Central role of defective apoptosis in autoimmunity. J Mol Endocrinol, **31**: 373-399.

Kulmala P, Savola K, Petersen JS, Vahasalo P, Karjalainen J, Lopponen T, Dyrberg T, Akerblom HK, & Knip M (1998) Prediction of insulin-dependent diabetes mellitus in siblings of

children with diabetes: A population-based study. The Childhood Diabetes in Finland Study Group. J Clin Invest, **101**: 327-336.

Kurtzke JF, Beebe GW, & Norman JE Jr (1979) Epidemiology of multiple sclerosis in U.S. veterans: 1. Race, sex, and geographic distribution. Neurology, **29**: 1228-1235.

Kuwabara S (2004) Guillain-Barre syndrome: epidemiology, pathophysiology and management. Drugs, **64**: 597-610.

Lacey JV, Laing TJ, Gillipsie BW, & Schottenfeld D (1997) Re: Epidemiology of scleroderma among women: assessment of risk from exposure to silica and silicone. J Rheum, **24**: 1853-1854 (Letter).

Lacey JV, Garabrant DH, Laing TJ, Gillespie BW, Mayes MD, Cooper BC, & Schottenfeld D (1999) Petroleum distillate solvents as risk factors for undifferentiated connective tissue disease (UCTD). Am J Epidemiol, **149**: 761-770.

Ladona MG, Izquierdo Martinez M, Posada de la Paz M, de la Torre R, Ampurdanes C, Segura J, & Sanz EJ (2001) Pharmacogenetic profile of xenobiotic enzyme metabolism in survivors of the Spanish Toxic oil syndrome. Environ Health Perspect, **109**: 369-375.

LaGasse JM, Brantley MS, Leech NJ, Rowe RE, Monks S, Palmer JP, Nepom GT, McCulloch DK, & Hagopian WA (2002) Successful prospective prediction of type 1 diabetes in schoolchildren through multiple defined autoantibodies: an 8-year follow-up of the Washington State Diabetes Prediction Study. Diabetes Care, **25**: 505-511.

Lahoz C, del Pozo V, Gallardo S, Cardaba B, Jurado A, Cortegano MI, del Amo A, Arrieta I, & Palomino P (1997) Immunological aspects of the Toxic oil syndrome. Berlin, Heidelberg, Springer Verlag.

Laing TJ, Gillespie BW, Toth MB, Mayes MD, Gallavan RH Jr, Burns CJ, Johanns JR, Cooper BC, Keroack BJ, Wasko MC, Lacey JV Jr, & Schottenfeld D (1997) Racial differences in scleroderma among women in Michigan. Arthritis Rheum, **40**(4): 734-742.

Lambert N & Nelson JL (2003) Microchimerism in autoimmune disease: more questions than answers? Autoimmunity Rev, **2**:133-139.

Lander ES & Schork NJ (1994) Genetic dissection of complex traits. Science, **265**: 2037-2048.

Landtblom AM, Floden U, Söderfeldt B, Wolfson C, & Axelson O (1996) Organic solvents and multiple sclerosis: a synthesis of the current evidence. Epidemiology, **7**: 429-433.

Lane TH & Burns SA (1996) Silica, silicon and silicones….unraveling the mystery. Curr Top Microbiol Immunol, **210**: 3-12.

Lane SE, Watts RA, Bentham G, Innes NJ, & Scott DG (2003) Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum, **48**: 814-823.

Langer P, Tajtakova M, Fodor G, Kocan A, Bohov P, Michalek J, & Kreze A (1998) Increased thyroid volume and prevalence of thyroid disorders in an area heavily polluted by polychlorinated biphenyls. Eur J Endocrinol, **139**(4): 402-409.

Langer P, Tajtakova M, Guretzki HJ, Kocan A, Petrik J, Chovancova J, Drobna B, Jursa S, Pavuk M, Trnovec T, Sebokova E, & Klimes I (2002) High prevalence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in employees at a polychlorinated biphenyl production factory. Arch Environ Health, **57**(5): 412-415.

Langer P, Kocan A, Tajtakova M, Petrik J, Chovancova J, Drobna B, Jursa S, Pavuk M, Koska J, Trnovec T, Sebokova E, & Klimes I (2003) Possible effects of polychlorinated biphenyls and organochlorinated pesticides on the thyroid after long-term exposure to heavy environmental pollution. J Occup Environ Med, **45**(5): 526-532.

Langworth S, Bjorkman L, Elinder CG, Jarup L, & Savlin P (2002) Multidisciplinary examination of patients with illness attributed to dental fillings. J Oral Rehabil, **29**: 705-713.

Lauwerys RR, Bernard A, Roels HA, Buchet J-P, & Viau C (1984) Characterization of cadmium proteinuria in man and rat. Environ Health Perspect, 54: 147-152.

Lawrence DA & McCabe MJ (1995) Immune modulation by toxic metals. In: Goyer RA, Klaassen CD, & Waalkes MP eds. Metal toxicology. Academic Press, pp 305-337.

Lawrence DA, Mudzinski S, Rusofsky U, & Warner G (1987) Mechanisms of metal-induced immunotoxicity. In: Berlin A, Dean J, Draper MH, Smith EMB, & Spreafico F eds. Immunotoxicology, Dordrecht, Martinus-Nijhoff, pp 293-307.

Lawson BR, Baccala R, Song J, Croft M, Kono DH, Theofilopoulos AN (2004) Deficiency of the cyclin kinase inhibitor p21 (WAF-1/CIP-1) promotes apoptosis of activated/memory T cells and inhibits spontaneous systemic autoimmunity. J Exp Med, **199**: 547-557.

Layland LE et al. (2004) Drug-induced autoantibody formation in mice: triggering by primed CD4+CD25- T cells, prevention by primed CD4+CD25+ T cells. Eur J Immunol, **34**(1): 36-46.
Lebwohl M (2003) Psoriasis. Lancet, **361**: 1197-1204.

Lee AY et al. (2004) Genetic polymorphism of cytochrome P450 2C9 in diphenylhydantoin-induced cutaneous adverse drug reactions. Eur J Clin Pharmacol, **60**(3): 155-159.

Leffel EK, Wolf C, Poklis A, & White KL Jr (2003) Drinking water exposure to cadmium, an environmental contaminant, results in the exacerbation of autoimmune disease in the murine model. Toxicology, **188**: 233-250.

Leiba A, Amital H, Gershwin ME, & Shoenfeld Y (2001) Diet and lupus. Lupus, **10**: 246-248.

Leiter EH (1982) Multiple low-dose streptozotocin-induced hyperglycemia and insulitis in C57BL mice: influence of inbred background, sex, and thymus. Proc Natl Acad Sci (USA), **79**(2): 630-634.

Lemire JM, Archer DC, Beck L, & Spiegelberg HL (1995) Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. J Nutr, **125**(6): 1704S-1708S.

Levine S & Sowinski R (1980) Enhancement of allergic encephalomyelitis by particulate adjuvants inoculated long before antigen. Am J Pathol, **99**: 291-304.

Levine JS, Branch DW, & Rauch J (2002) The antiphospholipid syndrome. N Engl J Med, **346**: 752-763.

Li M & Boyages SC (1994) Iodide induced lymphocytic thyroiditis in the BB/W rat: evidence of direct toxic effects of iodide on thyroid subcellular structure. Autoimmunity, **18**(1): 31-40.

Li J, Johansen C, Bronnum-Hansen H, Stenager E, Koch-Henriksen N, & Olsen J (2004a) The risk of multiple sclerosis in bereaved patients: A nationwide cohort study in Denmark. Neurology, **62**: 726-729.

Li FK, Tse KC, Lam MF, Yip TP, Lui SL, Chan GS, Chan KW, Chan EY, Choy BY, Lo WK, Chan TM, & Lai KN (2004b) Incidence and outcome of antiglomerular basement membrane disease in Chinese. Nephrology (Carlton), **9**: 100-104.

Liu Z (2002) Are anti-BP180 IgG1 or IgG4 autoantibodies pathogenic? J Invest Dermatol, **119**: 989-990.

Liu G, Schwartz JA, & Brooks SC (2000) Estrogen receptor protects p53 from deactivation by human double minute-2. Cancer Res, **60**: 1810-1814.

Loftus EV Jr (2004) Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology, **126**: 1504-1517.

Long SA, Van de Water J, & Gershwin ME (2002) Antimitochondrial antibodies in primary biliary cirrhosis: the role of xenobiotics. Autoimmunol Rev, **1**: 37-42.

Loose LD, Silkworth JB, Pittman KA, Benitz KF, & Mueller W (1978) Impaired host resistance to endotoxin and malaria in polychlorinated biphenyl- and hexachlorobenzene-treated mice. Infect Immun, **20**: 30-35.

Lorenzi M, Cagliero E, & Schmidt NJ (1985) Racial differences in incidence of juvenile-onset type 1 diabetes: epidemiologic studies in southern California. Diabetologia, **28**: 734-738.

Lugowski SJ, Smith DC, Bonek H, Lugowski J, Peters W, & Seple J (2000) Analysis of silicon in human tissues with special reference to silicone breast implants. J Trace Elements Med Biol, **14**: 31-42.

Lundin KE, Scott H, Hansen T, Paulsen G, Halstensen TS, Fausa O, Thorsby E, & Sollid LM (1993) Gliadin-specific, HLA-DQ (alpha 1*0501, beta 1*0201) restricted T cells isolated from the small intestinal mucosa of celiac disease patients. J Exp Med, **178**: 187-196.

Luo G et al. (2002) CYP3A4 induction by drugs: correlation between a pregnane X receptor reporter gene assay and CYP3A4 expression in human hepatocytes. Drug Metab Dispos, **30**(7): 795-804.

Luster MI, Hayes HT, Korach K, Tucker AN, Dean JH, Greenlee WF, & Boorman GA (1984) Estrogen immunosuppression is regulated through estrogenic responses in the thymus. J Immunol, **133**: 110-116.

Luster MI, Simeonova PP, Galluci R, & Matheson J (1999) Autoimmunity and risk assessment. Environ Health Perspect, **107**(suppl 5): 679-680.

Lovas K & Husebye ES (2002) High prevalence and increasing incidence of Addison's disease in western Norway. Clin Endocrinol (Oxford), **56**(6): 787-791.

Lundberg I, Alfredsson L, Plato N, Sverdrup B, Klareskog L, & Kleinau S (1994) Occupation, occupational exposure to chemicals and rheumatological disease. Scand J Rheumatol, **23**: 305-310.

Lykissa ED, Kala SV, Hurley JB, & Lebovitz RM (1997) Release of low molecular weight silicones and platinum from silicone breast implants. Anal Chem, **69**: 4912-4916.

Lytton SD, Helander A, Zhang-Gouillon ZQ, Stokkeland K, Bordone R, Arico S, Albano E, French SW, & Ingelman-Sundberg M (1999) Autoantibodies against cytochromes P-4502E1 and P-4503A in alcoholics. Mol Pharmacol, **55**: 223-233.

McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, & Kwoh CK (1995) Incidence of systemic lupus erythematosus: Race and gender differences. Arthritis Rheum, **38**: 1260-1270.

McConnachie PR & Zahalsky AC (1991) Immunological consequences of exposure to pentachlorophenol. Arch Environ Health, **46**(4): 249-253.

McConnachie PR & Zahalsky AC (1992) Immune alterations in humans exposed to the termiticide technical chlordane. Arch Environ Health, **47**(4): 295-301.

McCrae KR, Bussel JB, Mannucci PM, Remuzzi G, & Cines DB (2001) Platelets: an update on diagnosis and management of thrombocytopenic disorders. Hematology (Am Soc Hematol Educ Program), **2001**: 282-305.

McDevitt H, Singer S, & Tisch R (1996) The role of MHC class II genes in susceptibility and resistance to type I diabetes mellitus in the NOD mouse. Horm Metab Res, **28**(6): 287-288.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, & Wolinsky JS (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol, **50**: 121-127.

McDowell TL, Symons JA, Ploski R, Forre O, & Duff GW (1995) A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1α polymorphism. Arthritis Rheum, **38**: 221-228.

McMichael A & Hall AJ (1997) Ultaviolet radiation: explaining the “latitude” effect in multiple sclerosis? Epidemiology, **8**: 642-645.

McMurray R, Keisler D, Kanuckel K, Izui S, & Walker SE (1991) Prolactin influences autoimmune disease activity in the female B/W mouse. J Immunol, **147**: 3780-3787.

McMurray RW, Weidensaul D, Allen SH, & Walker SE (1995) Efficacy of bromocriptine in an open label therapeutic trial for systemic lupuserythematosus. J Rheumatol. **22**: 2084-2091.

Madsen KM, Lauritsen MB, Pedersen CB et al. (2003) Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics, **112**: 604-606.

Magistrelli C et al. (1999) Polymorphic genotypes of the HRES-1 human endogenous retrovirus locus correlate with systemic lupus erythematosus and autoreactivity. Immunogenetics, **49**: 829-834.

Maharaj SVN (2004) Platinum concentration in silicone breast implant material and capsular tissue by ICP-MS. Anal Bioanal Chem, **380**: 84-89.

Maibach H (1975) Acute laryngeal obstruction presumed secondary to thimerosal (Merthiolate) delayed hypersensitivity. Contact Dermatitis, **1:** 221.

Maksymowych WP, Suarez-Almazor M, Chou CT, & Russell AS (1995) Polymorphism in the LMP2 gene influences susceptibility to extraspinal disease in HLA-B27 positive individuals with ankylosing spondylitis. Ann Rheum Dis, **54**: 321-324.

Manger K, Repp R, Jansen M, Geisselbrecht M, Wassmuth R, Westerdaal NAC, Pfahlberg A, Manger B, & van de Winkel JGJ. Fcγ receptor IIa, IIIa and IIIb polymorphisms in German patients with systemic lupus erythematosus: association with clinical symptoms. Ann Rheum Dis, **61**: 786-792.

Manns MP & Obermayer-Straub P (1997) Cytochromes p450 and uridine triphosphate-glucuronosyltransferases: Model autoantigens to study drug-induced, virus-induced, and autoimmune liver disease. Hepatol, **26**: 1054-1066.

Marchetti B, Morale MC, Testa N, Tirolo C, Caniglia S, Amor S, Dijkstra CD, & Barden N (2001) Stress, the immune system and vulnerability to degenerative disorders of the central nervous system in transgenic mice expressing glucocorticoid receptor antisense RNA. Brain Res Rev, **37**: 259-272.

Margolin L (2003) Non-L-tryptophan related eosinophilia-myalgia syndrome with hypoproteinemia and hypoalbuminemia. J Rheumatol, **30**: 628-629.

Marie I, Hatron PY, Levesque H et al. (1999) Influence of age on characteristics of polymyositis and dermatomyositis in adults. Medicine (Baltimore), **78**: 139-147.

Martel P & Joly P (2001) Pemphigus: autoimmune diseases of keratinocyte's adhesion molecules. Clin Dermatol, **19**: 662-674.

Martinez A, Fernández-Arquero M, Pascual-Salcedo D, Conejero L, Alves H, Balsa A, & de la Concha EG (2000) Primary association of tumor necrosis factor-region genetic markers with susceptibility to rheumatoid arthritis. Arthritis Rheum, **43**: 1366-1370.

Martyn CN, Cruddas M, & Compston DA (1993) Symptomatic Epstein-Barr virus infection and multiple sclerosis. J Neurol Neurosurg Psychiatry, **56**: 167-168.

Masi AT & Chrousos GP (1996) Hypothalamic-pituitary-adrenal-glucocorticoid axis function in rheumatoid arthritis. J Rheumatol, **23**: 577-581.

Mason JW (2003) Myocarditis and dilated cardiomyopathy: an inflammatory link. Cardiovasc Res, **60**: 5-10.

Masson MJ & Uetrecht JP (2004) Tolerance induced by low dose D-penicillamine in the brown Norway rat model of drug-induced autoimmunity is immune-mediated. Chem Res Toxicol, **17**(1): 82-94.

Matarese G, Sanna V, Lechler RI, Sarvetnick N, Fontana S, Zappacosta S, & La Cava A (2002) Leptin accelerates autoimmune diabetes in female NOD mice. Diabetes, **51**: 1356-1361.

Matheson D, Clarkson T, & Gelfand E (1980) Mercury toxicity (acrodynia) induced by long-term injection of gamma globulin. J Pediatr, **97**: 153-155.

Mathieson PW et al. (1991) Immunoregulation of mercuric chloride-induced autoimmunity in Brown Norway rats: a role for CD8+ T cells revealed by *in vivo* depletion studies. Eur J Immunol, **21**(9): 2105-2109.

Matsui T, Kurokawa M, Kobata T, Oki S, Azuma M, Tohma S, Inoue T, Yamamoto K, Nishioka K, & Kato T (1999) Autoantibodies to T cell co-stimulatory molecules in systemic autoimmune diseases. J Immunol, **162**: 4328.

Mattey DL, Daws PT, Gonzalez-Gay MA, Garcia-Porrua C, Thomson W, Hajeer AH, & Ollier WER (2001) HLA-DRB1 alleles encoding an aspartic acid at position 70 protect against developing of rheumatoid arthritis. J Rheumatol, **28**: 232-239.

Matzinger P (1994) Tolerance, danger, and the extended family. Annu Rev Immunol, **12**: 991-1045.

May DG, Black CM, Olsen NJ, Csuka ME, Tanner SB, Bellino L, Porter JA, Wilkinson Gr, Branch RA. (1990) Scleroderma is associated with differences in individual routes of drug metabolism: a study with dapsone, debrisoquin and mephenytoin. Clin Pharmacol Ther, **49**: 286-295.

Mayeno AN, Belongia EA, Lin F, Lundy SK, & Gleich GJ (1992) 3-(Phenylamino)alanine, a novel aniline-derived amino acid associated with the eosiniphilia-myalgia syndrome: a link to the toxic oil syndrome? Mayo Clin Proc, **67**: 1134-1139.

Mayeno AN, Benson LM, Naylor S, Colberg-Beers M, Puchalski JT, & Gleich GJ (1995) Biotransformation of 3-(phenylamino)-1,2-propanediol to 3-(phenylamino)alanine: A chemical link between toxic oil syndrome and eosinophilia-myalgia syndrome. Chem Res Toxicol, **8**: 911-916.

Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, & Schottenfeld D (2003) Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum, **48**: 2246-2255.

Meera P, Rao PR, Shanker R, & Tripathi O (1992) Immunomodulating effects of gamma-HCH (lindane) in mice. Immunopharmacol Immunotoxicol, **14**: 261-282.

Mehlhorn J, Enderlein G, Conrad K, & Ziegler V (1999) Analysis for the association between progressive systemic scleroderma, exposure to quartz dust and silicosis in East German uranium mining. Zbl Arbeitsmed, **49**: 134-147.

Mellai M, Giordano M, D'Alfonso S, Marchini M, Scorza R, Giovanna Danieli M, Leone M, Ferro I, Liguori M, Trojano M, Ballerini C, Massacesi L, Cannoni S, Bomprezzi R, & Momigliano-Richiardi P (2003) Prolactin and prolactin receptor gene polymorphisms in multiple sclerosis andsystemic lupus erythematosus. Hum Immunol, **64**: 274-284.

Mendez EP, Lipton R, Ramsey-Goldman R, Roettcher P, Bowyer S, Dyer A, & Pachman LM (2003) NIAMS Juvenile DM Registry Physician Referral Group. US incidence of juvenile dermatomyositis, 1995-1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. Arthritis Rheum, **49**(3): 300-305.

Merkel PA (2001) Drug-induced vasculitis. Rheum Dis Clin North Am, **27**: 849-862.

Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, & Saag KG (2004) Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum, **50**(1): 72-77.

Meyer RP et al. (2001a) Oxidative hydrolysis of scoparone by cytochrome p450 CYP2C29 reveals a novel metabolite. Biochem Biophys Res Commun, **285**(1): 32-39.

Meyer RP et al. (2001b) Possible function of astrocyte cytochrome P450 in control of xenobiotic phenytoin in the brain: *in vitro* studies on murine astrocyte primary cultures. Exp Neurol, **167**(2): 376-384.

Michielsen CP, Bloksma N, Ultee A, van Mil F, & Vos JG (1997) Hexachlorobenzene-induced immunomodulation and skin and lung lesions: a comparison between Brown Norway, Lewis, and Wistar rats. Toxicol Appl Pharmacol, **144**(1): 12-26.

Michielsen CC, van Loveren H, & Vos JG (1999a) The role of the immune system in hexachlorobenzene-induced toxicity. Environ Health Perspect, **107**(Suppl 5): 783-792.

Michielsen CC, Bloksma N, Klatter FA, Rozing J, Vos JG, & van Dijk JE (1999b) The role of thymus-dependent T cells in hexachlorobenzene-induced inflammatory skin and lung lesions. Toxicol Appl Pharmacol, **161**: 180-191.

Michielsen C, Boeren S, Rietjens I, van Mil F, Vos J, & Bloksma N (2000) The mercapturic acid biotransformation pathway of hexachlorobenzene is not involved in the induction of splenomegaly, or skin and lung lesions in the Brown Norway rat. Arch Toxicol, **74**: 609-617.

Michielsen C, Zeamari S, Leusink-Muis A, Vos J, & Bloksma N (2002) The environmental pollutant hexachlorobenzene causes eosinophilic and granulomatous inflammation and *in vitro* airways hyperreactivity in the Brown Norway rat. Arch Toxicol, **76**: 236-247.

Michielsen CP, Leusink-Muis A, Vos JG, & Bloksma N (2001) Hexachlorobenzene-induced eosinophilic and granulomatous lung inflammation is associated with *in vivo* airways hyperresponsiveness in the Brown Norway rat. Toxicol Appl Pharmacol, **172**: 11-20.

Miller AS 3rd, Willard V, Kline K, Tarpley S, Guillotte J, Lawler FH, & Pendell GM 3rd (1998) Absence of longitudinal changes in rheumatologic parameters after silicone breast implantation: a prospective 13-year study. Plast Reconstr Surg, **102**: 2299-2303.

Minami Y, Sasaki T, Arai Y, Kurisu Y, & Hisamichi S (2003) Diet and systemic lupus erythematosus: a 4 year prospective study of Japanese patients. J Rheumatol, **30**: 747-754.

Mirtcheva J et al. (1989) Immunological alterations inducible by mercury compounds. III. H-2A acts as an immune response and H-2E as an immune "suppression" locus for HgCl2-induced antinucleolar autoantibodies. Eur J Immunol, **19**(12): 2257-2261.

Miyaura H & Iwata M (2002) Direct and indirect inhibition of Th1 development by progesterone and glucocorticoids. J Immunol, **168**: 1087-1094.

Modzelewski JR, Greene WB, Sobieski M, & Raso DS (1996) Silicone detection in fat globules in pericapsular tissue of women and rats augmented with silicone gel. Breast J, **4**: 275-280.

Mohr DC, Hart SL, Julian L, Cox D, & Pelletier D (2004) Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. Brit Med J, **328**: 731-736.

Monestier M, Novick KE, & Losman MJ (1994) D-penicillamine- and quinidine-induced antinuclear antibodies in A.SW (H-2s) mice: similarities with autoantibodies in spontaneous and heavy metal-induced autoimmunity. Eur J Immunol, **24**(3): 723-730.

Mongey AB & Hess E (2001) *In vitro* production of antibodies to histones in patients receiving chronic procainamide therapy. J Rheumatol, **28**(9): 1992-1998.

Monzoni A, Masutti F, Saccoccio G, Bellentani S, Tiribelli C, & Giacca M (2001) Genetic determinants of ethanol-induced liver damage. Mol Med, **7**: 255-262.

Mordes JP, Desemone J, &Rossini AA (1987) The BB rat. Diabetes Metab Rev, **3**(3): 725-750.

Mortensen JT, Brønnum-Hansen, & Rasmussen K (1998) Multiple sclerosis and organic solvents. Epidemiology, **9**: 168-174.

Mu H, Charmley P, King MC, & Criswell LA 1996) Synergy between T cell receptor ß gene polymorphism and HLA-DR4 in susceptibility to rheumatoid arthritis. Arthritis Rheum, **39**: 931-937.

Mueller PW, Paschal DC, Hammel RR, Klincewicz SL, MacNeil ML, Spierto B, & Steinberg KK (1992) Chronic renal effects in three studies of men and women occupationally exposed to cadmium. Arch Environ Contam Toxicol, **23**: 125-136.

Muller H, de Toledo FW, & Resch KL (2001) Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. Scand J Rheumatol, **30**: 1-10.

Mulloy KB (2003) Silica exposure and systemic vasculitis. Environ Health Perspect, **111**(16): 1933-1938.

Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, & Ascherio A (2004) Vitamin D intake and incidence of multiple sclerosis. Neurology, **62**: 60-65.

Murphy RB & Vodyanoy V (1982) Fatty acid anilides and the Toxic oil syndrome. Lancet, Jan 30;1(8263):98.

Murray J (2002) Infection as a cause of multiple sclerosis. Brit Med J, **325**: 1128.

Nagata S & Suda T (1995) Fas and Fas ligand: lpr and gld mutations. Immunol Today, **16**: 39-43.

Nagayama J, Tsuji H, Iida T, Hirakawa H, Matsueda T, & Ohki M (2001) Effects of contamination level of dioxins and related chemicals on thyroid hormone and immune response systems in patients with "Yusho". Chemosphere, **43**: 1005-1010.

Nagi AH & Khan AH (1984) Gold nephropathy in rabbits using an indigenous preparation. A morphological study. Intern Urol Nephrol, **16**: 49-59.

Nagi AH, Alexander F, & Barabas AZ (1971) Gold nephropathy in rats. Light and electron microscopic studies. Exp Mol Pathol, **15**: 354-362.

Naim JO & van Oss CJ (1995) Silicone gels as adjuvants. Effects on humoral and cell-mediated immune responses. Adv Exp Med Biol, **383**: 1-6.

Naim JO, Lanzafame RJ, & van Oss CJ (1995a) The effect of silicone-gel on the immune response. J Biomater Sci Polym Ed, **7**: 123-132.

Naim JO, Ippolito ML. Lanzafame RJ, & Van Oss CJ (1995b) Induction of type II collagen arthritis in the DA rat using silicone gels and oils as adjuvants. J Autoimmun, **8**: 751-761.

Naim JO, Ippolito KM, & Van Oss CJ (1997) Adjuvancy effect of different types of silicone gel. J Biomed Mater Res, **46**: 132-134.

Naim JO, Satoh M, Buehner NA, Ippolito KM, Yoshida H, Nusz D, Kurtelawicz L, Cramer SF, & Reeves WH (2000) Induction of hypergammaglobulinemia and macrophage activation by silicone gels and oils in female A.SW mice. Clin Diagn Immunol, **7**: 366-370.

Naisbitt DJ et al. (2001) Antigenicity and immunogenicity of sulphamethoxazole: demonstration of metabolism-dependent haptenation and T-cell proliferation *in vivo*. Br J Pharmacol, **133**(2): 295-305.

Nakken B, Jonsson R, & Bolstad AI (2001) Polymorphisms of the Ro52 gene associated with anti-Ro 52-kd autoantibodies in patients with primary Sjögren's syndrome. Arthritis Rheum, **44**: 638-646.

Neidhart M (1997) Bromocriptine has little direct effect on murine lymphocytes, the

immunomodulatory effect being mediated by the suppression of prolactin secretion. Biomed Pharmacother, **51**: 118-125.

Neidhart M (1998) Prolactin in autoimmune diseases. Proc Soc Exp Biol Med, **217**: 408-419.

Nepom GT (1993) Immunogenetics and IDDM. Diabetes Rev, **1**: 93-103.

Nepom GT (1998) Major histocompatibility complex-directed susceptibility to rheumatoid arthritis. Adv Immunol, **68**: 315-332.

Neuberger J (1998) Halothane hepatitis. Eur J Gastroenterol Hepatol, **10**: 631-633.

Nicholson JJ, Wong GE, Frondoza CG, & Rose NR (1996) Silicone gel and octamethylcyclotetrasiloxane potentiate antibody production to bovine serum albumin in mice. Curr Top Microbiol Immunol, **210**: 139-144.

Nielsen JB & Hultman P (2002) Mercury-induced autoimmunity in mice. Environ Health Perspect, **110**(Suppl 5): 877-881.

Nierkens S et al. (2002) Selective requirement for CD40-CD154 in drug-induced type 1 versus type 2 responses to trinitrophenyl-ovalbumin. J Immunol, **168**(8): 3747-3754.

Nierkens S et al. (2004) Evaluation of the use of reporter antigens in an auricular lymph node assay to assess the immunosensitizing potential of drugs. Toxicol Sci, **79**(1): 90-97.

Nietert PJ, Sutherland SE, Silver RM, Pandey JP, Knapp RG, Hoel DG, & Dosemeci M (1998) Is occupational organic solvent exposure a risk factor for scleroderma? Arthritis Rheum, **41**: 1111-1118.

Nisipeanu P & Korxzyn AD (1993) Psychological stress as risk factor for exacerbations in multiple sclerosis. Neurology, **43**: 1311-1312.

Noli C, Koeman JP, & Willemse T (1995) A retrospective evaluation of adverse reactions to trimethoprim-sulphonamide combinations in dogs and cats. Vet Q, **17**(4): 123-128.

Noller KL, Blair PB, O'Brien PC, & Mellon LJ (1988) Increased occurrence of autoimmune disease among women exposed *in utero* to diethylstilbestrol. Fertil Steril, **49**: 1080-1082.

Noone RB (1997) A review of the possible health implications of silicone breast implants. Cancer, **79**: 1747-1756.

Nowack R, Flores-Suarez LF, & van der Woude FJ (1998) New developments in pathogenesis of systemic vasculitis. Curr Opin Rheumatol, **10**: 3-11.

Nuyts GD, Vlem EV, Vos AD, Daelemans RA, Rovive G, Elseviers MM, Schurgers M, Segaert M, D'Haese PC, & De Broe ME (1995) Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. Nephrol Dialysis Trans, **10**: 1162-1165.

Nyren O, Yin L, Josefsson S, McLaughlin JK, Blot WJ, Engqvist M, Hakelius L, Boice JD, & Adami HO (1998) Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. Br Med J, **316**: 417-422.

Ochel M et al. (1991) IL-4 is required for the IgE and IgG1 increase and IgG1 autoantibody formation in mice treated with mercuric chloride. J Immunol, **146**(9): 3006-3011.

Oen K (2000) Comparative epidemiology of the rheumatic diseases in children. Curr Opin Rheumatol, **12**(5): 410-414.

Offit PA & Hackett CA (2003) Addressing parents' concerns: Do vaccines cause allergic or autoimmune diseases? Pediatrics, **111**(3): 653-659.

Ogilvie GK et al. (1988) Hypotension and cutaneous reactions associated with intravenous administration of etoposide in the dog. Am J Vet Res, **49**(8): 1367-1370.

Ohsawa M (1993) Nutritional and toxicological implication of trace elements in the immune response. In: Prasad AS ed. Essential and toxic elements in human health and disease: An update. Prog Clin Biol Res, **380**: 283-298.

O'Hanlon TP, Lawless OJ, Katzin WE, Feng LJ, & Miller FW (2000) Restricted and shared patterns of TCR beta-chain gene expression in silicone breast implant capsules and remote sites of tissue inflammation. J Autoimmun, **14**: 283-293.

Ohsawa M, Takahashi K, & Otsuka F (1988) Induction of anti-nuclear antibodies in mice orally exposed to cadmium at low concentrations. Clin Exp Immunol, **73**: 98-102.

Ohsawa M, Otsuka F, & Takahashi K (1990) Modulation of the immune response by trace elements. In: Tomita H ed. Trace elements in clinical medicine. Tokyo, Springer-Verlag, pp 165-171.

Okada K et al. (2001) Phenytoin promotes Th2 type immune response in mice. Clin Exp Immunol, **124**(3): 406-413.

Oldstone MB (1987) Molecular mimicry and autoimmune disease. Cell, **50**: 819-820.

Oliver DW, Walker MS, Walters AE, Chatrath P, & Lamberty BGH (2000) Anti-silicone antibodies and silicone breast implants. Br J Plast Surg, **53**: 410-414.

Olofsson P et al. (2003) Identification and isolation of dominant susceptibility loci for pristane-induced arthritis. J Immunol, **171**(1): 407-416.

Olsson AR, Skogh T, Axelson O, & Wingren C (2004) Occupations and exposures in the work environment as determinants for rheumatoid arthritis. Occup Environ Med, **61**(3) : 233-238.

Otsuki T, Sakaguchi H, Tomokuni A, Aikoh T, Matsuki T, Kawakami Y, Kuaska M, Ueki H, Kita S, & Ueki A (1998) Soluble Fas mRNA is dominantly expressed in cases with silicosis. Immunology, **94**: 258-262.

Owen CJ, Jennings CE, Imrie H, Lachaux A, Bridges NA, Cheetham TD, & Pearce SH (2003) Mutational analysis of the FOXP3 gene and evidence for genetic heterogeneity in the immunodysregulation, polyendocrinopathy, enteropathy syndrome. J Clin Endocrin Metab, **88**: 6034-6039.

Oya H, Kawamura T, Shimizu T, Bannai M, Kawamura H, Minagawa M, Watanbe H, Hatakeyama K, & Abo T (2000) The differential effect of stress on natural killer T (NKT) and NK cell function. Clin Exp Immunol, **121**: 384-390.

Pablos JL, Santiago B, Galindo M, Carreira PE, Ballestin C, & Gomez-Reino JJ (1999) J Pathol, **88**: 63-68.

Padyukov L, Silva C, Stolt P, Alfredsson L, & Klareskog L (2004) A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum, **50**: 3085-3089.

Paivonsalo-Hietanen T, Tuominen J, Saari KM. (2000). Uveitis in children: population-based study in Finland. Acta Ophthalmol Scand, **78**: 84-88.

Park Y, Moon Y, & Chung HY (2003) AIRE-1 (autoimmune regulator type 1) as a regulator of the thymic induction of negative selection. Ann NY Acad Sci, **1005**: 431-435.

Parks CG, Conrad K, & Cooper GS (1999) Occupational exposure to crystalline silica and autoimmune disease. Environ Health Perspect, **107**(Suppl 5): 793-802.

Parks CG, Cooper GS, Nylander-French LA, Sanderson WT, Dement JM, Cohen PL, Dooley, MA, Treadwell EL, St Clair EW, Gilkerson GS, Hoppin JA, & Savitz DA (2002) Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: a population-based, case-control study in the southeastern United States. Arthritis Rheum, **46**: 1840-1850.

Paronetto F (1993) Immunologic reactions in alcoholic liver disease. Semin Liver Dis, **13**: 183-195.

Pastor JC, Puente B, Telleria J, Carrasco B, Sanchez H, & Nocito M (2001) Antisilistic antibodies in patients with silicone implants for retinal detachment surgery. Ophthalmic Res, **33**: 87-90.

Pattison DJ, Harrison RA, & Symmons DP (2004) The role of diet in susceptibility to rheumatoid arthritis: a systematic review. J Rheumatol, **31**: 1310-1319.

Pearce EN, Farwell AP, & Braverman LE (2003) Thyroiditis. N Engl J Med, **348**: 2646-2655.

Pearson CM (1956) Development of arthritis, periarthritis and periostitis in rats given adjuvants. Proc Soc Exp Biol Med, **91**(1): 95-101.

Pedotti R, Mitchell D, Wedemeyer J et al. (2001) An unexpected version of horror autotoxicus: anaphylactic shock to a self-peptide. Nature Immunol, **2**: 216-222.

Pellegrini I, Lebrun JJ, Ali S, & Kelly PA (1992) Expression of prolactin and its receptor in human lymphoid cells. Mol Endocrinol, **6**: 1023-1031.

Pelletier L et al. (1987) HgCl2 induces nonspecific immunosuppression in Lewis rats. Eur J Immunol, **17**(1): 49-54.

Pelletier L et al. (1990) Role of CD8+ T cells in mercury-induced autoimmunity or immunosuppression in the rat. Scand J Immunol, **31**(1): 65-74.

Peltonen J, Varga J, Solberg S, Uitto J, & Jimenez S (1991) Elevated expression of the genes for transforming growth factor-Beta 1 and type IV collagen in diffuse fasciitis associated with the eosinophilia-myalgia syndrome. J Invest Dermatol, **96**: 20-25.

Perkins LL, Clark BD, Klein PJ, & Cook RR (1995) A meta-analysis of breast implants and connective tissue disease. Ann Plast Surg, **35**: 561-570.

Pernis B & Paronetto F (1962) Adjuvant effects of silica (tridymite) on antibody production. Proc Soc Exp Biol Med, **110**: 390-392.

Peschken CA & Esdaile JM (2000) Systemic lupus erythematosus in North American Indians: a population based study. J Rheumatol, **27**(8): 1884-1891.

Peter JB & Shoenfeld Y (1996) Autoantibodies. Amsterdam, Elsevier Science.

Peters W (1998) Correspondence. Rupture of silicone gel implants. Lancet, **351**: 521.

Peters H, Cripps D, Gocmen A, Bryan G, Erturk E, & Morris C (1987) Turkish epidem ic hexachlorobenzene porphyria: A 30-year study. Ann NY Acad Sci, **514**: 183-190.

Petri M, Howard D, & Repke J (1991) Frequency of lupus flare in pregnancy: The Hopkins Lupus Pregnancy Center experience. Arthritis Rheum, **34**: 1538-1545.

Pfau JC, Brown JM, & Holian A (2004) Silica-exposed mice generate autoantibodies to apoptotic cells. Toxicology, **195**: 167-176.

Pfleiederer B, Ackerman JL, & Garrido L (1993) Migration and biodegradation of free silicone from silicone gell filled implants after long term implantation. Magn Reson Med, **30**: 534-543.

Philen R, and Dicker R. TOS (Toxic Oil Syndrome) An Epidemic of Mass Proportions in Spain, 1981. Case Studies in Applied Epidemiology. No.002-800 (2000). Centers for Disease Control and Prevention, National Center for Environmental Health. 1 May 2005 http://iier.isciii.es/ea/pdf/ea_tos1.htm.

Philen RM, Posada de la Paz M, Hill RH, Schurz HH, Abaitua Borda I, Gomez de la Camara A, & Kilbourne EM (1997) Epidemiology of the Toxic oil syndrome. Berlin, Heidelberg, Springer Verlag.

Phillips SC, Petrone RL, & Hemstreet GP (1988) A review of the non-neoplastic kidney effects of hydrocarbon exposure in humans. Occup Med, **3**: 495-509.

Picha GJ & Goldstein JA (1991) Analysis of the soft –tissue response to components used in the manufacture of breast implants: rat animal model. Plast Reconstr Surg, **87**: 490-500.

Pichler WJ (2003) Drug-induced autoimmunity. Curr Opin Allergy Clin Immunol, **3**: 249-253.

Pieters R & Albers R (1999) Screening tests for autoimmune-related immunotoxicity. Environ Health Perspect, **107**(Suppl 5): 673-677.

Pietsch P, Vohr H-W, Degitz K, & Gleichmann E (1989) Immunological alterations inducible by mercury compounds. II. $HgCl_2$ and gold sodium thiomalate enhance serum IgE and IgG concentrations in susceptible mouse strains. Int Arch Allergy Appl Immunol, **90**: 47-53.

Pillemer SR, Matteson EL, Jacobsson LT, Martens PB, Melton LJ 3rd, O'Fallon WM, & Fox PC (2001) Incidence of physician-diagnosed primary Sjogren syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proc, **76**(6): 593-599.

Pirmohamed M & Park BK (2001) HIV and drug allergy. Curr Opin Allergy Clin Immunol, **1**(4): 311-316.

Pittoni V & Valesini G (2002) The clearance of apoptotic cells: implications for autoimmunity. Autoimmunity Rev, **1**: 154-161.

Pittoni V & Valesini G (2002) The clearance of apoptotic cells: implications for autoimmunity. Autoimmunity Rev,**1**: 154-61.

Pociot F, Briant L, Jongeneel CV, Mølvig J, Worsaae H, Abbal M, Thomsen M, Nerup J, & Cambon-Thomsen A (1993) Association of tumor necrosis factor (TNF) and class II major histocompatibility complex alleles with the secretion of TNFα and TNFβ by human mononuclear cells: a possible link to insulin-dependent diabetes mellitus. Eur J Immunol, **23**: 224-231.

Podolsky DK (2002) Inflammatory bowel disease. N Engl J Med, **347**: 417-429.

Pollard KM & Landberg GP (2001) The *in vitro* proliferation of murine lymphocytes to mercuric chloride is restricted to mature T cells and is interleukin 1 dependent. Int Immunopharmacol, **1**: 581-593.

Pollard KM, Pearson DL, Hultman P, Hildebrandt B, & Kono DH (1999) Lupus-Prone mice as models to study xenobiotic-induced acceleration of systemic autoimmunity. Environ Health Perspect, **107**(Suppl 5): 729-735.

Ponsonby AL, McMichael A, & van der Mei I (2002) Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology, **181-182**: 71-78.

Popovic M et al. (2004) Investigating the role of 2-phenylpropenal in felbamate-induced idiosyncratic drug reactions. Chem Res Toxicol, **17**(12): 1568-1576.

Posada de la Paz M, Abaitua Borda I, Kilbourne EM, Tabuenca Oliver J, Diaz de Rojas F, & Castro Garcia M (1989) Late cases of Toxic oil syndrome: Evidence that the aetiological agent persisted in oil stored for up to one year. Food Chem Toxicol, **27**: 517-521.

Posada de la Paz M, Philen RM, Abaitua Borda I, Sicilia Socias JM, Gomez de la Camara A, & Kilbourne EM (1996) Toxic oil syndrome: Traceback of the toxic oil and evidence for a point source epidemic. Food Chem Toxicol, **34**: 251-257.

Poulas K, Tsibri E, Kokla A, Papanastasiou D, Tsouloufis T, Marinou M, Tsantili P, Papapetropoulos T, & Tzartos SJ (2001) Epidemiology of seropositive myasthenia gravis in Greece. J Neurol Neurosurg Psychiatry, **71**(3) : 352-356.

Povey A, Guppy MJ, Wood M, Knight C, Black CM, & Silman AJ (2001) Cytochrome P2 polymorphism and susceptibility to scleroderma following exposure to organic solvents. Arthritis Rheum, **44**: 662-665.

Powell J, Van de Water J, Gershwin E. (1999)Evidence for the Role of Environmental Agents in the Initiation or Progression of autoimmune conditions. Environ Health Perspect, 107 Suppl 5: 667-77.

Pozzilli P, Manfrini S, & Monetini L (2001) Biochemical markers of type 1 diabetes: clinical use. Scand J Clin Lab Invest, **61**(Suppl 235): 38-44.

Prentice LM, Phillips DIW, Sarsero D, Beever K, McLachlan SM, & Smith B (1990) Geographical distribution of subclinical autoimmune thyroid disease in Britain: a study using highly sensitive direct assays for autoantibodies to thyroglobulin and thyroid peroxidase. Acta Endocrinol, **123**: 493-498.

Prins JB et al. (1991) Genetic variation within and between lines of diabetes-prone and non-diabetes-prone BB rats; allele distribution of 8 protein markers. Lab Anim, **25**(3): 207-211.

Prokunina L, Padyukov L, Bennet A, de Faire U, Wiman B, Prince J, Alfredsson L, Klareskog L, & Alarcón-Riquelme M (2004) Association of the PD-1.3A allele of the PDCD1 gene in patients with rheumatoid arthritis negative for rheumatoid factor and the shared epitope. Arthritis Rheum, **50**: 1770-1773.

Pugliese A, Zeller M, Fernandez A Zalcberg LJ, Bartlett RJ, Ricordi C, Pietropaolo M, Eisenbarth GS, Bennett ST, Patel DD. (1997) The insulin gene is transcribed in the human thymus and transcription levels correlate with allelic variation at the INS VNTR-IDDM2 susceptibility locus for type I diabetes. Nat Genet, **15**: 293-297.

Pugliese A, Brown D, Garza D Murchison D, Zeller M, Redondo M, Diez J, Eisenbarth GS, Patel DD, Ricordi C. (2001) Self-antigen presenting cells expressing islet cell molecules in human thymus and peripheral lymphoid organs: phenotypic characterization and implications for immunological tolerance and type 1 diabetes. J Clin Invest, **107**: 555-564.

Qasim FJ, Thiru S, & Gillespie K (1997) Gold and D-penicillamine induce vasculitis and up-regulate mRNA for IL-4 in the Brown Norway rat: support for a role for Th2 cell activity. Clin Exp Immunol, **108**(3): 438-445.

Quddus J, Johnson KJ, Gavalchin J, Amento EP, Chrisp CE, Yung RL, & Richardson BC (1993) Treating activated CD4+ T cell with either of two distinct DNA methyltransferase inhibitors, 5-azacytidine or procainamide, is sufficient to cause lupus-like disease in syngeneic mice. J Clin Invest, **92**(1): 38-53.

Queiroz MLS & Dantas DCM (1997) B Lymphocytes in mercury-exposed workers. Pharmacol Toxicol, **81**: 130-133.

Queiroz MLS, Perlingeiro RCR, Dantas DCM, Annichino Bizzacchi JM, & De Capitani EM (1994) Immunoglobulin levels in workers exposed to inorganic mercury. Pharmacol Toxicol, **74**: 72-75.

Queiroz ML, Bincoletto C, Perlingeiro RC, Quadros MR, & Souza CA (1998a) Immunoglobulin levels in workers exposed to hexachlorobenzene. Hum Exp Toxicol, **17**: 172-175.

Queiroz ML, Quadros MR, Valadares MC, & Silveira JP (1998b) Polymorphonuclear phagocytosis and killing in workers occupationally exposed to hexachlorobenzene. Immunopharmacol Immunotoxicol, **20**: 447-454.

Quero C, Colome N, Prieto MR, Carrascal M, Posada de la Paz M, Gelpi E, & Abian J (2004) Determination of protein markers in human serum: Analysis of protein expression in Toxic oil syndrome studies. Proteomics, **4**: 303-315.

Ramenghi U, Bonissoni S, Migliaretti G, DeFranco S, Bottarel F, Gambaruto C, DiFranco D, Priori R, Conti F, Dianzani I, Valesini G, Merletti F, & Dianzani U (2000) Deficiency of the Fas apoptosis pathway without Fas gene mutations is a familial trait predisposing to development of autoimmune diseases and cancer. Blood, **95**: 3176-3182.

Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, Sundin U, & van Venrooij WJ (2003) Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum, **48**: 2741-2749.

Rasooly L, Burek CL, & Rose NR (1996) Iodine-induced autoimmune thyroiditis in NOD-H2^{h4} mice. Clin Immunol Immunopathol, **81**(3): 287-292.

Raucy JL (2003) Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. Drug Metab Dispos, **31**(5): 533-539.

Ravindra K, Bencs L, & Van Grieken R (2004) Platinum group elements in the environment and their health risk. Sci Total Environ, **318**: 1-43.

Reed T, Page WF, Viken RJ, & Christian JC (1996) Genetic predisposition to organ-specific endpoints of alcoholism. Alcohol Clin Exp Res, **20**: 1528-1533.

Reggiani G (1978) Medical problems raised by the TCDD contamination in Seveso, Italy. Arch Toxicol, **40**: 161-168.

Regius O, Lengyel E, Borzsonyi L, & Eregi E (1988) The effect of smoking on the presence of antinuclear antibodies and on the morhology of lymphocytes in aged subjects. Z Gerontol, **21**: 161-163.

Regius O, Rajczy K, Gergely I, Borzsonyi L, Lengyel E, & Vargha P (1990) The effect of smoking on perispheral blood lymphoctyes and on some immunological parameters of old age. Z Gerontol, **23**: 163-167.

Renzoni E, Lympany P, Sestini P, Pantelidis P, Wells A, Black C, Welsh K, Brunn C, Knight C, Foley P, & du Bois RM (2000) Distribution of novel polymorphisms of the interleukin-8 and CXC receptor 1 and 2 genes in systemic sclerosis and cryptogenic fibrosing alveolitis. Arthritis Rheum, **43**: 1633-1640.

Rhie JW, Han SB, Byeon JH, Ahn ST, & Kim HM (1998) Efficient *in vitro* model for immunotoxicologic assessment of mammary silicone implants. Plast Reconstr Surg, **102**: 73-77.

Rhodes J, Chen H, Hall SR, Beesley JE, Jenkins DC, Collins P, & Zheng B (1995) Therapeutic potententiation of the immune system by costimulatory Schiff-base-forming drugs. Nature (Lond), **270**: 21433-21436.

Richardson BC (2002) Role of DNA methylation in the regulation of cell function: autoimmunity, aging, cancer. J Nutr, **132**: 2401S-2405S.

Richardson BC (2003) DNA methylation and autoimmune disease. Clin Immunol, **109**: 72-79.

Richardson B, Scheinbart L, Strabler J, Gross L, Hanash S, & Johnson M (1990) Evidence for impaired T cell DNA methylation in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum, **33**: 1665-1673.

Richardson BC, Stranler JR, Pivirotto TS, Quddus J, Bayliss GE, Gross LA et al. (1992) Phenotypic and functional similarities between 5-azacytidine-treated Tcells and T cell subset in patients with active systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum, **35**: 647-662.

Rider LG, Artlett CM, Foster CB, Ahmed A, Neeman T, Chanock SJ, Jimenez SA, & Miller FW, for the Childhood Myositis Heterogeneity Collaborative Study Group (2000) Polymorphisms in the IL-1 receptor antagonist gene VNTR are responsible risk factors for juvenile idiopathic inflammatory myopathies. Clin Exp Immunol, **121**: 47-52.

Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IAG, Debatin KM, Fischer A, & de Villarty JP (1995) Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. Science, **268**: 1347-1349.

Rieux-Laucat F, Blachère S, Danielan S, de Villarty JP, Oleastro M, Solary E, Bader-Meunier B, Arkwright P, Pondaré C, Bernaudin F, Chapel H, Nielsen S, Berrah M, Fischer A, & Le Deist F (1999) Lymphoproliferative syndrome with autoimmunity: A possible genetic basis for dominant expression of the clinical manifestations. Blood, **94**: 2575-2582.

Riise T, Nortvedt MW, & Ascherio A (2003) Smoking is a risk factor for multiple sclerosis. Neurology, **61**: 1122-1124.

Riskind PN, Massacesi L, Doolittle TH, Hauser SL. The role of prolactin in autoimmune demyelination: suppression of experimental allergic encephalomyelitis by bromocriptine. Ann Neurol. 1991 May;29(5):542-7.

Robinson CJ, Balazs T, & Egorov IK (1986) Mercuric chloride-, gold sodium thiomalate-, and D-penicillamine-induced antinuclear antibodies in mice. Toxicol Appl Pharmacol, **86**(2): 159-169.

Rodgers K (1997) Effects of oral administration of malathion on the course of disease in MRL-lpr mice. J Autoimmun, **10**: 367-373.

Rodgers KE & Ellefson DD (1990) Modulation of respiratory burst activity and mitogenic response of human peripheral blood mononuclear cells and murine splenocytes and peritoneal cells by malathion. Appl Toxicol, **14**: 309-317.

Rodgers K & Xiong S (1996) Contribution of mast cell mediators in macrophage function after malathion administration. Fundam Appl Toxicol, **33**: 100-108.

Rodgers K & Xiong S (1997a) Effect of acute administration of malathion by oral and dermal routes on serum histamine levels. Int J Immunopharmacol, **19**: 437-441.

Rodgers K & Xiong S (1997b) Effect of administration of malathion for 90 days on macrophage function and mast cell degranulation. Toxicol Lett, **93**: 73-82.

Rodgers KE, Leung N, Devens B, Ware CF, & Imamura T (1986) Lack of immunosuppressive effects of acute and subacute administration of malathion on murine cellular and humoral immune responses. Pest Biochem Physiol, **25**: 358-365.

Rodringuez-Perez M, Gonzalez-Dominguez J, Mataran L, Garcia-Perez S, & Salvatierra D (1994) Association of HLA-DR5 with mucocutaneous lesions in patients with rheumatoid arthritis receiving gold sodium thiomalate. J Rheumatol, **21**: 41-43.

Ronningen KS, Spurkland A, Tait BD, Drummond B, Lopez-Larrea C, Baranda FS, Menendez-Diaz MJ, Caillat-Zucman S, Beaurain G, Garchon HJ, Ilonen J, Reijonen H, Knip M, Boehm BO, Rosak C, Loliger C, Kuhnl P, Ottenhoff T, Contu L, Carcassi C, Savi M, Zanelli P, Neri TM, Hamaguchi K, Kimura A, Dong RP, Chikuba N, Nagataki S, Gorodezky C, Debaz H, Robles C, Coimbra HB, Martinho A, Ruas MA, Sachs JA, Garcia-Pachedo M, Biro A, Nikaein A, Dombrausky L, Gonwa T, Zmijewski C, Monos D, Kamoun M, Layrisse Z, Magli MC, Balducci P, Thorsby E. (1992) HLA class II associations in insulin-dependent diabetes mellitus among Blacks, Caucasoids, and Japanese. In: Tsuji K, Aizawa A, & Sasazuki T eds. HLA 1991 - Proceedings of the 11th International Histocompatibility Workshop and Conference. Oxford, Oxford University Press, vol 1, pp 713-722.

Rood MJ, van Krugten MV, Zanelli E, van der Linden MW, Keijsers V, Schneuder GMT, Verduyn W, Westendorp RGJ, de Vries RRP, Breedveld FC, Verweij CL, & Huizinga TWJ (2000) TNF-308A and HLA-DR3 alleles contribute independently to susceptibility to systemic lupus erythematosus. Arthritis Rheum, **43**: 129-134.

Rosati G (2001) The prevalence of multiple sclerosis in the world: an update. Neurol Sci, **22**: 117-139.

Rose NR (1996) Foreword – The uses of autoantibodies. In: Shoenfeld Y & Peter JB ed. Autoantibodies. Amsterdam, Elsevier, pp xxvii-xxix.

Rose N & Mackay I, ed. (1998) The autoimmune diseases, 3rd ed. San Diego, Academic Press.

Rose NR, Hamilton RG, & Detrick B (2002a) Manual of clinical laboratory immunology. Washington, DC, ASM Press.

Rose NR, Bonita R, & Burek CL (2002b) Iodine: an environmental trigger of thyroiditis. Autoimmun Rev, **1**(1-2): 97-103.

Rosenberg NL (1996) The neuromythology of silicone breast implants. Neurology, **46**: 308-314.

Rosenberg AM, Semchuk KM, McDuffie HH, Ledingham DL, Cordeiro DM, Cessna AJ, Irvine DG, Senthilselvan A, & Dosman JA (1999) Prevalence of antinuclear antibodies in a rural population. J Toxicol Environ Health, **56**: 225-236.

Rosenblum MD, Olasz E, WoodliffJE, Johnson BD, Konkol MC, Gerber KA, Orentas RJ, Sandford G, & Truitt RL (2004) CD200 is a novel p53-target gene involved in apoptosis-associated immune tolerance. Blood, **103**: 2691-2698.

Rosenman, KD & Zhu Z (1995) Pneumoconiosis and associated medical conditions. Am J Ind Med, **27**: 107-113.

Rosenman KD, Moore-Fuller M, & Reilly MF (1999) Connective tissue disease and silicosis. Am J Ind Med, **25**: 375-381.

Rossini AA, Handler ES, Mordes JP, & Greiner DL (1995) Human autoimmune diabetes mellitus: lessons from BB rats and NOD mice--Caveat emptor. Clin Immunol Immunopathol, **74**(1): 2-9.

Rubin RL (1992) Autoantibody specificity in drug-induced lupus and neutrophil-mediated metabolism of lupus-inducing drugs. Clin Biochem, **25**(3): 223-234.

Rubin RL, Reimer G, Mcnally EM, Nusinow SR, Searles RP, & Tan EM (1986) Procainamide elicits a selective autoantibody immune response. Clin Exp Immunol, **63**(1): 58-67.

Rubin RL, Salomon DR, & Guerrero RS (2001) Thymus function in drug-induced lupus. Lupus, **10**(11): 795-801.

Ruiz-Irastorza G, Lima F, Alves J, Khamashta MA, Simpson J, Hughes GR, & Buchanan NM (1996) Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. Am J Rheumatol, **35**: 133-138.

Ruiz-Irastorza G, Khamashta MA, Gordon C, Lockshin MD, Johns KR, Sammaritano L, Hughes GR. Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. Arthritis Rheum. 2004 Feb 15;51(1):78-82.

Ruiz-Mendez M, Posada de la Paz M, Abian J, Calaf R, Blount B, Castro-Molero N, Philen RM, & Gelpi E (2001) Storage time and deordorization temperature influence the formation of aniline-derived compounds in denatured rapeseed oils. Food Chem Toxicol, **39**: 91-96.

Rutgers A, Heeringa P, Damoiseaux JG, & Cohen Tervaert JW (2003) ANCA and anti-GBM antibodies in diagnosis and follow-up of vasculitic disease. Eur J Intern Med, **14**: 287-295.

Sabharwal P, Glaser R, Lafuse W, Varma S, Liu Q, Arkins S, Kooijman R, Kutz L, Kelley KW, & Malarkey WB (1992) Prolactin synthesized and secreted by human peripheral blood mononuclear cells:an autocrine growth factor for lymphoproliferation. Proc Natl Acad Sci (USA), **89**: 7713-7716.

Sakabe K, Okuma M, Karaki S, Matsuura S, Yoshida T, Aikawa H, Izumi S, & Kayama F (1999) Inhibitory effect of natural and environmental estrogens on thymic hormone production in thymus epithelial cell culture. Int J Immunopharmacol, **21**: 861-868.

Sakaguchi S (2000) Animal models of autoimmunity and their relevance to human diseases. Curr Opin Immunol, **12**(6): 684-690.

Sakaguchi S & Sakaguchi N (1989) Organ-specific autoimmune disease induced in mice by elimination of T cell subsets. V. Neonatal administration of cyclosporin A causes autoimmune disease. J Immunol, **142**(2): 471-480.

Sala M, Sunyer J, Herrero C, To-Figueras J, & Grimalt J (2001) Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. Occup Environ Med, **58**(3): 172-177.

Sallsten G, Thoren J, Barregard L, Schutz A, & Skarping G (1996) Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. J Dent Res, **75**: 594-598.

Salomon B & Bluestone JA (2001) Complexities of CD28/B7 :CTLA-4 costimulatora pathways in autoimmunity and transplantation. Annu Rev Immunol, **19**: 225-252.

Sanchez Guerrero J, Schur PH, Sergent JS, & Liang MH (1994) Silicone breast implants and rheumatic disease. Clinical, immunologic, and epidemiologic studies. Arthritis Rheum, **37**: 158-168.

Sanchez Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, & Liang MH (1995) Silicone breast implants and the risk of connective-tissue diseases and symptoms. N Engl J Med, **332**: 1666-1670.

Sanchez-Margalet V, Martin-Romero C, Santos-Alvarez J, Goberna R, Najib S, & Gonzalez-Yanes C (2003) Role of leptin as an immunomodulator of blood mononuclear cells: mechanisms of action. Clin Exp Immunol, **133**: 11-19.

Sanchez-Porro Valades P, Posada de la Paz M, de Andres Copa P, Gimenez Ribota O, & Abaitua Borda I (2003) Toxic oil syndrome: Survival in the whole cohort between 1981 and 1995. J Clin Epidemiol, **56**: 701-708.

Sanchez-Roman J, Wichmann I, Salaberri J, Varela JM, & Nunez-Roldan A (1993) Multiple clinical and biological autoimmune manifestation in 50 workers after occupational exposure to silica. Ann Rheum Dis, **52**: 534-538.

Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, Zappacosta S, & Matarese G (2003) Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. J Clin Invest, **111**: 241-250

Savige J, Davies D, Falk RJ, Jennette JC, & Wiik A (2000) Antineutrophil cytoplasmic antibodies and associated diseases: a review of the clinical and laboratory features. Kidney Int, **57**: 846-862.

Saxe SR, Wekstein MW, Kryscio RJ *et al*. (1999) Alzheimer's disease, dental amalgam and mercury. J Am Dent Assoc, **130:** 191-199.

Schaefer CJ & Wooley PH (1999b) The influence of silicone implantation on murine lupus in MRL lpr/lpr mice. J Rheumatol, **26**: 2215-2221.

Schaefer CJ, Lawrence WD, & Wooley PH (1999) Influence of long term silicone implantation on type II collagen induced arthritis in mice Ann Rheum Dis, **58**: 503-509.

Schatz D, Krischer J, Horne G, Riley W, Spillar R, Silverstein J, Winter W, Muir A, Derovanesian D, Shah S, Malone J, & Maclaren N (1994) Islet cell antibodies predict insulin-dependent diabetes in United States school age children as powerfully as in unaffected relatives. J Clin Invest, **93**: 2403-2407.

Scheinfeld N (2003) Phenytoin in cutaneous medicine: its uses, mechanisms and side effects. Dermatol Online J, **9**(3): 6.

Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, & van Venrooij WJ (2000) The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum, **43**: 155-163.

Schellekens H (2003) Immunogenicity of therapeutic proteins. Nephrol Dial Transplant, **18**(7): 1257-1259.

Schenbart LS, Johnson MA, Gross LA, Edelstein SR, & Richardson BC (1991) Procainamide inhibits DNA methyltransferase in a human T cell line. J Rheumatol, **18**: 530-534.

Schielen P, Schoo W, Tekstra J, Oostermeijer HH, Seinen W, & Bloksma N (1993) Autoimmune effects of hexachlorobenzene in the rat. Toxicol Appl Pharmacol, **122**: 233-243.

Schielen P, Den Besten C, Vos JG, Van Bladeren PJ, Seinen W, & Bloksma N (1995a) Immune effects of hexachlorobenzene in the rat: role of metabolism in a 13-week feeding study. Toxicol Appl Pharmacol, **131**: 37-43.

Schielen P, Van Rodijnen W, Pieters RH, & Seinen W (1995b) Hexachlorobenzene treatment increases the number of splenic B-1-like cells and serum autoantibody levels in the rat. Immunology, **86**: 568-574.

Schmitt J & Papisch W (2002) Recombinant autoantigens. Autoimmun Rev, **1**: 79-88.

Schulmann D, Kubicka-Muranyi M, Mirtschewa J, Günther J, Kind P, & Gleichmann E (1990) Adverse immune reactions to gold. I. Chronic treatment with an Au(I) drug sensitizes mouse T

cells not to Au(I), but to Au(III) and induces autoantibody formation. J Immunol, **145**(7): 2132-2139.

Schuppe HC, Ronnau AC, Schmiedeberg SV, Ruzicka T, Gleichmann E, & Griem P (1998) Immunomodulation by heavy metal compounds. Clinics Dermatol, **16**: 149-157.

Schurz HH, Hill RH, Philen RM, Posada de la Paz M, Abaitua Borda I, Kilbourne EM, Bernert T, & Needham LL (1997) Analytical measurements of products of aniline and triglycerides in oil samples associated with the toxic oil syndrome. Berlin, Heidelberg, Springer Verlag.

Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, Cohen PL, Earp HS, Matsushima GK (2001) Phagocytosis and clearance of apoptotic cells is mediated by MER. Nature (Lond), **411**: 207-211.

Seidler A, Hellenbrand W, Robra B-P et al. (1996) Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology, **46:** 1275-1284.

Seiki K & Sakabe K (1997) Sex hormones and the thymus in relation to thymocyte proliferation and maturation. Arch Histol Cytol, **60**: 29-38.

Shah MS, Davies TF, & Stagnaro-Green A (2003) The thyroid during pregnancy: a physiological and pathological stress test. Minerva Endocrinol, **28**: 233-245.

Shaheen VM et al. (1999) Immunopathogenesis of environmentally induced lupus in mice. Environ Health Perspect, **107**(Suppl 5): 723-727.

Shanklin DR, Smalley DL, Hall MF, & Stevens MV (1996) T cell-mediated immune response to silica in silicone breast implant patients. Curr Top Microbiol Immunol, **210**: 227-236.

Sharma RP & Gehring PJ (1979) Immunologic effects of vinyl chloride in mice. Ann NY Acad Sci, **320**: 551-563.

Sheikh A, Smeeth L, & Hubbard R(2003) There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: Lack of support for the hygiene hypothesis. J Allergy Clin Immunol, **111**: 131-135.

Shenker BJ, Guo TL, & Shapiro LM (1998) Low-level methylmercury exposure causes human T-cells to undergo apoptosis-evidence of mitochondrial dysfunction. Environ Res, **77**: 149-159.

Shenton JM, Teranishi M, Abu-Asab MS, Yager JA, & Uetrecht JP (2003) Characterization of a potential animal model of an idiosyncratic drug reaction: Nevirapine-induced skin rash in the rat. Chem Res Toxicol, **16**: 1078-1089.

Shenton JM., Chen J, & Uetrecht JP (2004) Animal models of idiosyncratic drug reactions. Chem Biol Interact, **150**(1): 53-70.

Shevach EM (2000) Regulatory T cells in autoimmunity. Annu Rev Immunol, **18**: 423-449.

Shimada S, Yamauchi M, Takamatsu M, Uetake S, Ohata M, & Saito S (2002) Experimental studies on the relationship between immune responses and liver damage induced by ethanol after immunization with homologous acetaldehyde adducts. Alcohol Clin Exp Res, **26S**: 86-90.

Silbergeld EK & Devine PJ (2000) Mercury – are we studying the right endpoints and mechanisms. Fuel Process Technol, **65**(66): 35-42.

Siegmund W, Franke G, Biebler KE, Donner I, Kawellis R, Kairies M, Scherber A, & Huller H (1985) The influence of the acetylator phenotype on the clinical use of dihydralazine. Int J Clin Pharmacol Ther Toxicol, **23**: 74-78.

Silman AJ & Jones S (1992) What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? Ann Rheum Dis, **51**: 1322-1324.

Silverman BG, Brown SL, Bright RA, Kaczmarek RG, Arrowsmith Lowe JB, & Kessler DA (1996) Reported complications of silicone gel breast implants: an epidemiologic review. Ann Intern Med, **124**: 744-756.

Silverstein MJ, Handel N, Gamagami P, Gierson ED, Furmanski M, Collins AR, Epstein M, & Cohlan BF. (1992) Breast cancer diagnosis and prognosis in women following augmentation with silicone gel-filled prostheses. Eur J Cancer, **28**: 635-640.

Silverstone AE, Gavalchin J, & Gasiewicz TA (1998) TCDD, DES, and estradiol potentiate a lupus- like autoimmune nephritis in NZB x SWR (SNF_1) mice. Toxicologist, **42**: 403.

Sim E & Law SK (1985) Hydralazine binds covalently to complement component C4. Different reactivity of C4B gene products. FEBS Lett, **184**(2): 323-327.

Shinkai K et al. (1999) Mouse popliteal lymph node assay for assessment of allergic and autoimmunity-inducing potentials of low-molecular-weight drugs. J Toxicol Sci, **24**(2): 95-102.

Shoenfeld Y & Isenberg D ed. (1990) The mosaic of autoimmunity (The factors associated with autoimune diseases). Amsterdam, New York, Oxford, Elsevier.

Shoenfeld Y & Rose NR (2004) Infection and autoimmunity. Elsevier.

Sidransky H &Verney E (1994) Comparative studies on tryptophan binding to hepatic nuclear envelopes in Sprague-Dawley and Lewis rats. Am J Physiol, **267**: R502-R507.

Sidransky H &Verney E (1997) Mouse strain and source of L-tryptophan affects hepatic nuclear tryptophan binding. Toxicology, **118**: 37-47.

Siegmund W, Franke G, Biebler KE, Donner I, Kawellis R, Kairies M, Scherber A, & Huller H (1985) The influence of the acetylator phenotype on the clinical use of dihydralazine. Int J Clin Pharmacol Ther Toxicol, **23**: 74-78.

Silman AJ & Jones S (1992) What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? Ann Rheum Dis, **51**: 1322-1324.

Silman A, Kay A, & Brennan P (1992) Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum, **35**: 152-155.

Silver RM, Ludwicka A, Hampton M, Ohba T, Bingel SA, Smith T, Harley RA, Maize J, & Heyes M (1994) A murine model of the eosinophilia-myalgia syndrome induced by 1,1' ehylidenebis(L-tryptophan). J Clin Invest, **93**: 1473-1480.

Simat TJ, Kleeberg KK, Muller B, & Sierts A (1999) Synthesis, formation, and occurence of contaminants in biotechnically manufactured L-tryptophan. Adv Exp Med Biol, **467**: 469-480.

Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr, **21**: 495-505.

Skarstein K, Wahren M, Zaura E, Hattori M, & Jonsson R (1995) Characterization of T cell receptor repertoire and anti-Ro/SSA autoantibodies in relation to sialadenitis of NOD mice. Autoimmunity, **22**(1): 9-16.

Slavin RE, Swedo JL, Brandes D, Gonzalez-Vitale JC, & Osornio-Vargas A (1985) Extrapulmonary silicosis: a clinical, morphologic, and ultrastructural study. Hum Pathol, **16**: 393-312.

Sluis-Cremer, GK, Hessel PA, Hnizdo EH, Churchill AR, & Zeiss EA (1985) Silica, silicosis, and progressive systemic sclerosis. Br J Ind Med, **42**: 838-843.

Sluis-Cremer GK, Hessel PA, Hnizdo E, & Churchill AR (1986) Relationship between silicosis and rheumatoid arthritis. Thorax, **41**: 596-601.

Smalley DL, Shanklin DR, Hall MF, Stevens MV, & Hanissian A (1995) Immunologic stimulation of T lymphocytes by silica after use of silicone mammary implants. FASEB J, **9**: 424-427.

Smalley DL, Shanklin DR, & Hall MF (1998) Monocyte dependent stimulation of human T cells by silicon dioxide. Pathobiology, **66**: 302-305.

Smialowicz RJ (2002) The rat as a model in developmental immunotoxicology. Hum Exp Toxicol, **21**: 513-519.

Smiley JD & Moore SE Jr (1988) Molecular mechanisms of autoimmunity. Am J Med Sci, **295**(5): 478-496.

Smith W & Ball GV (1980) Lung injury due to gold treatment. Arthritis Rheum, **23**: 351-354.

Smith DA & Germolec DR (2000) Developmental exposure to TCDD and mercuric chloride in autoimmune-prone MRL/*lpr* mice. Toxicologist, **54**: 8.

Smith BJ & Holladay SD (1997) Immune alterations in geriatric mice dosed subacutely with diethylstilbestrol (DES). J Appl Toxicol, **17**: 265-271.

Snapp KR, Boyer DB, Peterson LC, & Svare CW (1989) The contributions of dental amalgam to mercury in blood. J Dent Res, **68:** 780-785.

Soldan SS, Alvarez Retuerto AI, Sicotte NL, & Voskuhl RR (2003) Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol. J Immunol, **171**: 6267-6274.

Sollid L & Thorsby E (1993) HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology, **105**: 910-922.

Sopori M (2002) Effects of cigarette smoke on the immune system. Nat Rev Immunol, **2**: 372-377.

Speirs C, Fielder AH, Chapel H, Davey NJ, & Batchelor JR (1989) Complement system protein C4 and susceptibility to hydralazine-induced systemic lupus erythematosus. Lancet, **1**(8644): 922-924.

Stagnaro-Green A (2002) Clinical review 152: Postpartum thyroiditis. Clin Endocrinol Metab, **87**: 4042-4047.

Staples JA, Ponsonby AL, Lim LL, & McMichael AJ (2003) Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect, **111**: 518-523.

Stein EC, Schiffer RB, Hall WJ, & Young N (1987) Multiple sclerosis and the workplace: report of an industry-based cluster. Neurology, **37**: 1672-1677.

Stejskal VD, Danersund A, Lindvall A et al. (1999) Metal-specific lymphocytes: biomarkers of sensitivity in man. Neuroendocrinol Lett, **20:** 289-298.

Stengel B, Cenee S, Limasset JC, Protois JC, Marcelli A, & Hemon D (1996) Glomerular nerphropathies and exposure to organic solvents – a case-control study. Bull Acad Natl Med, **180**: 871-879.

Stevens A, Ray A, Alansari A, Hajeer A, Thomson W, Donn R, Ollier WER, Worthington J, & Davis JRE (2001a) Characterization of a prolactin gene polymorphism and ist association with systemic lupus erythematosus. Arthritis Rheum, **44**: 2358-2366.

Stevens A, Ray DW, Worthington J, & Davis JR (2001b) Polymorphisms of the human prolactin gene--implications for production oflymphocyte prolactin and systemic lupus erythematosus. Lupus, **10**: 676-683.

Stewart SF, Leathart JB, Chen Y, Daly AK, Rolla R, Vay D, Mottaran E, Vidali M, Albano E, & Day CP (2002) Valine-alanine manganese superoxide dismutase polymorphism is not associated with alcohol-induced oxidative stress or liver fibrosis. Hepatology, **36**: 1355-1360.

Stiller-Winkler R, Radaszkiewicz T, & Gleichmann E (1988) Immunopathological signs in mice treated with mercury compounds: I. Identification by popliteal lymph node assay of responder and nonresponder strains. Int J Immunopharmacol, **10**: 475-484.

Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, Alfredsson L & the EIRA Study Group (2003) Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis, **62**: 835-841.

Straton K, Gable A, & McCormick MC (2001) Thimerosal-containing vaccines and neurodevelopmental disorders. Washington, DC, Institute of Medicine.

Stratta P, Mazzucco G, Griva S, Tetta C, & Monga G (1988) Immune-mediated glomerulonephritis after exposure to paraquat. Nephron**, 48**: 138-141.

Stratta P, Messuerotti A, Canavese C, Coen M, Luccoli L, Bussolati B, Giorda L, Malavenda P, Cacciabue M, Bugiani M, Bo M, Ventura M, Camussi G, & Fubini B (2001) The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. Sci Total Environ, **270**: 179-190.

Strieder TGH, Prummel MF, Tijssen JGP, Endert E, & Wiersinga WM (2003) Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. Clin Endocrinol, **59**: 396-401.

Sturfelt G, Hellmer G, & Truedsson L (1996) TNF microsatellites in systemic lupus erythematosus – a high frequency of the TNFabc 2-3-1 haplotype in multicase SLE families. Lupus, **5**: 618-622.

Suciu I, Drejman I, & Valeskai M (1963) Contribution to the study of the diseases caused by vinyl chloride. Med Intern, **15**: 967-978.

Sundick RS et al. (1987) The incorporation of dietary iodine into thyroglobulin increases its immunogenicity. Endocrinology, **120**(5): 2078-2084.

Suneja T & Belsito D (2001) Thimerosal in the detection clinically relevant allergic contact reactions. J Am Acad Pathol, **45**: 23-27.

Susol E, Rands AL, Herrick A, McHugh N, Barrett JH, Ollier WER, & Worthington J (2000) Association of markers for TGFß3, TGFß2 and TIMP1 with systemic sclerosis. Rheumatology, **39**: 1332-1336.

Sutcliffe N, Clarke AE, Gordon C, Farewell V, & Isenberg DA (1999) The association of socio-economic status, race, psychosocial factors and outcome in patients with systemic lupus erythematosus. Rheumatology (Oxford), **38**(11): 1130-1137.

Suzuki S, Tourkina E, Ludwicka A, Hampton M, Bolster M, Maize J, & Silver RM (1996) A contaminant of L-tryptophan enhances expression of dermal collagen in a murine model of eosinophilia myalgia syndrome. Proc Assoc Am Physicians, **104**: 315-322.

Suzuki A, Yamada R, Chang X, Tokuhiro S, Sawada T, Suzuki M, Nagasaki M, Nakayama-Hamada M, Kawaida R, Ono M, Ohtsuki M, Furukawa H, Yoshino S, Yukioka M, Tohma S, Matsubara T, Wakitani S, Teshima R, Nishioka Y, Sekine A, Iida A, Takahashi A, Tsunoda T, Nakamura Y, Yamamoto K. (2003) Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. Nature Genet, **34**: 395-402.

Swanson SJ et al. (2004) Evaluation of methods to detect and characterize antibodies against recombinant human erythropoietin. Nephron Clin Pract, **96**(3): c88-95.

Swygert LA, Maes EF, Sewell LE, Miller L, Falk H, & Kilbourne EM (1990) Eosinophilia-myalgia syndrome. J Am Med Assoc, **264**: 1698-1703.

Szeto C, Gillespie KM, & Mathieson PW (1999) Low-dose mercuric chloride induces resistance in brown norway rats to further mercuric chloride by up-regulation of interferon-gamma. Scand J Immunol, **50**(2): 195-201.

Tabuenca JM (1981) Toxic-allergic syndrome caused by ingestion of rapeseed oil denatured with aniline. Lancet, **2**: 567-568.

Takagi H, Ochoa MS, Zhou L, Helfman T, Murata H, & Falanga V (1995) Enhanced collagen synthesis and transcription by peak E: A contaminant of L-tyrptophan preparations associated with the eosinophilila myalgia syndrome epidemic. J Clin Invest, **96**: 2120-2125.

Takamatsu M, Yamauchi M, Maezawa Y, Saito S, Mawyama S, & Uchikoshi T (2000) Genetic polymorphisms of interleukin-1β in association with the development of alcoholic liver disease in Japanese patients. Am J Gastroenterol, **95**: 1305-1311.

Takeuchi K, Turkey SJ, Tan EM, & Pollard KM (1995) Analysis of the autoantibody response to fibrillarin in human disease and murine models of autoimmunity. J Immunol, **154**: 961-971.
Talwalkar JA & Lindor KD (2003) Primary biliary cirrhosis. Lancet, **362**: 53-61.

Tamaki H, Itoh E, Kaneda T, Asahi K, Mitsuda N, Tanizawa O, & Amino N (1993) Crucial role of serum human chorionic gonadotropin for the aggravation of thyrotoxicosis in early pregnancy in Graves' disease. Thyroid, **3**: 189-193.

Tan EM, Feltkamp TEW, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, Gordon T, Hardin JA, Kalden JR, Lahita RG, Maini RN, McDougal JS, Rothfield NF, Smeenk RJ, Takasaki E, Whik A, Wilson MR, & Koziol JA (1997) Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum, **40**: 1601-1611.

Taneja V & David CS (1999) HLA Class II transgenic mice as models of human diseases. Immunol Rev, **169**: 67-79.

Taurog JD et al. (1999) Inflammatory disease in HLA-B27 transgenic rats. Immunol Rev, **169**: 209-223.

Ten Tusscher GW, Steerenberg PA, Van Loveren H, Vos JG, Von dem Borne AEGK, Westra M, Van der Slikke JW, Olie K, Pluim HJ, & Koppe JG (2003) Peersistent hematologic and immunologic disturbances in 8-year-old Dutch children associated with perinatal dioxin exposure. Environ Health Perspect, **111**: 1519-1523.

Tena G (1982) Fatty acid anilides and the Toxic oil syndrome. Lancet, Jan 30;1(8263): 98.

Tenenbaum SA, Rice JC, Espinoza LR, Cuéllar ML, Plymale DR, Sander DM, Williamson LL, Haïslip AM, Gluck OS, Tesser JRP, Nogy L, Stribrny KM, Bevan JA & Garry RF. (1997a) Use of antipolymer antibody assay in recipients of silicone breast implants. Lancet, **349**: 449-454.

Tenenbaum SA, Rice JC, Espinoza LR, & Garry RF (1997b) Antipolymer antibodies, silicone breast implants, and fibromyalgia. Author's reply. Lancet, **349**: 1172-1173.

Terracini B (2004) The limits of epidemiology and the Spanish Toxic oil syndrome. Int J Epidemiol, **33**: 443-444.

Thiele GM, Tuma DJ, Willis MS, Vidali M, Stewart SF, Rolla R, Daly AK, Chen Y, Mottaran E, Jones DE, Leatherhart JB, Day CP, & Albano E (2003) Genetic and epigenetic factors in autoimmune reactions toward cytochrome P4502E1 in alcoholic liver disease. Hepatology, **37**: 410-419.

Thomas C et al. (1989) Popliteal lymph node reactions in mice induced by the drug zimeldine. Int J Immunopharmacol, **11**(6): 693-702.

Thomas C et al. (1990) Popliteal lymph node enlargement and antibody production in the mouse induced by zimeldine and related compounds with varying side chains. Int J Immunopharmacol, **12**(5): 561-568.

Thompson CB (1995) Distinct roles for the co-stimulatory ligands B7-1 and B7-2 in T helper cell differentiation? Cell, **81**: 979-982.

Thomson W, Harrison B, Ollier B, Wiles N, Payton T, Barrett J, Symmons D, & Silman A (1999) Quantifying the exact role of HLA-DRB1 alleles in susceptibility to inflammatory polyarthritis. Arthritis Rheum, **42**: 757-762.

Thrasher JD, Madison R, & Broughton A (1993) Immunologic abnormalities in humans exposed to chlorpyrifos: preliminary observations. Arch Environ Health, **48**(2): 89-93.

Timmer A (2003) Environmental influences on inflammatory bowel disease manifestations. Lessons from epidemiology. Dig Dis, **21**: 91-104.

Todhunter J & Farrow M (1998) Current scientific considerations in regard to defining a "silicone syndrome"/disease and the formation of silica from silicone. Int J Toxicol, **17**: 449-463.

Toh BH, van Driel IR, & Gleeson PA (1997) Pernicious anemia. N Engl J Med, **337**: 1441-1448.

Tomer Y(2002) Genetic dissection of familial autoimmune thyroid diseases using whole genome screening. Autoimmun Rev, **1**: 198-204.

Tomer Y, Greenberg DA, Concepcion E, Ban Y, & Davies TF (2002) Thyroglobulin is a thyroid specific gene for the familial autoimmune thyroid diseases. J Clin Endocrinol Metab, **87**: 404-407.

Tomita Y, Jyonouchi H, Engelman RW, Day NK, & Good RA (1993) Preventive action of carotenoids on the development of lymphadenopathy and proteinuria in MRL-lpr/lpr mice. Autoimmunity, **16**: 95-102.

Törnroth T & Skrifvars B (1974) Gold nephropathy prototype of membranous glomerulonephritis. Am J Pathol, **75**: 573-586.

Torres B, Aguilar F, Franco E, Sánchez E, Sánchez-Roman J, Alonso JJ, Núnez-Roldán A, Martín J, & González-Escribano MF (2004) Association of the CT60 marker of the CTLA4 gene with systemic lupus erythematosus. Arthritis Rheum, **50**: 2211-2215.

Tournade H et al. (1990) D-penicillamine-induced autoimmunity in Brown-Norway rats: Similarities with HgCl2-induced autoimmunity. J Immunol, **144**(8): 2985-2991.

Tournade H, Guery J-C, Pasquier R, Nochy D, Hinglais N, Guilbert B, Druet P, & Pelletier L (1991) Experimental gold-induced autoimmunity. Nephrol Dial Transplant, **6**: 621-630.

Tremlett HL, Evans J, Wiles CM, & Luscombe DK (2002) Asthma and multiple sclerosis: an inverse association in a case-control general practice population. Q J Med, **95**: 753-756.

Trepanier LA (2004) Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. J Vet Pharmacol Ther, **27**(3): 129-138.

Tsai HM (2003) Advances in the pathogenesis, diagnosis, and treatment of thrombotic thrombocytopenic purpura. J Am Soc Nephrol, **14**: 1072-1081.

Tsai HM & Lian EC (1998) Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med, **339**: 1585-1594.

Tsankov N, Stransky L, Kostowa M, Mitrowa T, & Obreschkowa E (1990) Induced pemphigus caused by occupational contact with Basochrom. Dermatosen Beruf Umbelt - Occup Environ Dermat, **38**: 91-93.

Tsao BP (2003) The genetics of human systemic lupus erythematosus. Trends Immunol, **24**: 595-602.

Tugwell P, Wells G, Peterson J, Welch V, Page J, Davison C, McGowan J, Ramroth D, & Shea B (2001) Do silicone breast implants cause rheumatologic disorders? A systematic review for a court-appointed national science panel. Arthritis Rheum, **44**: 2477-2484.

Turner S & Cherry N (2000) Rheumatoid arthritis in workers exposed to silica in the pottery industry. Occup Environ Med, **57**(7): 443-447.

Ueda S, Wakashin M, Wakashin Y, Yoshida H, Iesato K, Mori T, Mori Y, Akikusa B, & Okuda K (1986) Experimental gold nephropathy in guinea pigs: detection of autoantibodies to renal tubular antigens. Kidney Int, **29**: 539-548.

Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain, G Rainbow DB, Hunter KM, Smith AN, Di Genova G, Herr MH, Dahlman I, Payne F, Smyth D, Lowe C, Twells RC, Howlett S, Healy B, Nutland S, Rance HE, Everett V, Smink LJ, Lam AC, Cordell HJ, Walker NM, Bordin C, Hulme J, Motzo C, Cucca F, Hess JF, Metzker ML, Rogers J, Gregory S, Allahabadia A, Nithiyananthan R, Tuomilehto-Wolf E, Tuomilehto J, Bingley P, Gillespie KM, Undlien DE, Ronningen KS, Guja C, Ionescu-Tirgoviste C, Savage DA, Maxwell AP, Carson DJ, Patterson CC, Franklyn JA, Clayton DG, Peterson LB, Wicker LS, Todd JA, Gough SC. (2003) Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature (Lond), **423**: 506–511.

Ueki A, Yamaguchi M, Ueki H, Watanabe Y, Ohsawa G, Kinugawa K, Kawakami Y, & Hyodoh F (1994) Polyclonal human T-cell activation by silicate *in vitro*. Immunology, **82**: 332-335.

Uetrecht J (1990) Drug metabolism by leukocytes and its role in drug-induced lupus and other idiosyncratic drug reactions. Crit Rev Toxicol, **20**(4): 213-235.

Uetrecht JP (1997) Current trends in drug-induced autoimmunity. Toxicology, **119**: 37-43.

Vaarala O, Alfthan G, Jauhianen M, Leirsalo-Repo M, Aho K, & Palosuo T (1993) Crossreaction between antibodies to oxidized low-density lipoprotein and to cardiolipin in systemic lupus erthematosus. Lancet, **341**: 923-925.

Vagenakis AG & Braverman LE (1975) Adverse effects of iodides on thyroid function. Med Clin North Am, **59**: 1075-1088.

Vaisberg MW, Kaneno R, Franco MF, & Mendes NF (2000) Influence of cholecalciferol (vitamin D3) on the course of experimental systemic lupus erythematosus in F1 (NZBxW) mice. J Clin Lab Anal, **14**: 91-96.

Vaishnaw AK, McNally JD & Elkon KB (1997) Apoptosis in the rheumatic diseases. Arthritis Rheum, **40**: 1917-1927.

Valenti L, De Feo T, Fracanzani AL, Fatta E, Salvagnini M, Arico S, Rossi G, Fiorelli G, Fargion S. (2004) Cytotoxic T-lymphocyte antigen-4 A49G polymorphism is associated with susceptibility to and severity of alcoholic liver disease in Italian patients. Alcohol Alcohol. 39(4):276-80.

Vallyathan V, Shi XL, & Dalal NS (1988) ESR evidence for the hydroxyl radical formation in aqueous suspension of quartz particles and its possible significance to lipid peroxidation in silicosis. J Toxicol Environ Health, **25**: 237-245.

Van Amerongen BM, Dijkstra CD, Lips P, & Polman CH (2004) Multiple sclerosis and vitamin D: an update. Eur J Clin Nutr, **58**: 1095-1109.

Vandebriel RJ, Meredith C, Scott MP, van Dijk M, & van Loveren H (2000) Interleukin-10 is an unequivocal Th2 parameter in the rat, whereas interleukin-4 is not. Scand J Immunol, **52**: 519-524.

Van Der Mei IAF, Ponsonby A-L, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, & Kilpatrick T (2003) Past exposure to sun, skin phenotype, and risk of multiple sclerosis: a case-control study. Brit Med J, **327**: 316-322.

Van der Pol WL & van de Winkel JGJ (1998) IgG receptor polymorphisms: risk factors for disease. Immunogenetics, **48**: 222-232.

Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, Young ET. (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxford), **43**: 55-68.

VandeVord PJ, Gupta N, Wilson RB, Vinuya RZ, Schaefer CJ, Canady AI, & Wooley PH (2004) Immune reactions associated with silicone-based ventriculo-peritoneal shunt malfunctions in children. Biomaterials, **25**: 3835-3860.

Van Ommen B, van Bladeren PJ, Temmink JH, & Muller F (1985) Formation of pentachlorophenol as the major product of microsomal oxidation of hexachlorobenzene. Biochem Biophys Res Commun, **126**: 25-32.

Van Ommen B, Adang AE, Brader L, Posthumus MA, Muller F, & van Bladeren PJ (1986) The microsomal metabolism of hexachlorobenzene. Origin of the covalent binding to protein. Biochem Pharmacol, **35**: 3233-3238.

van't Veen AJ & van Joost T (1994) Sensitization to thimerosal (Merthilate) is still present today. Contact Dermatitis, **31:** 293-298.

van Vliet E et al. (1993) MHC control of IL-4-dependent enhancement of B cell Ia expression and Ig class switching in mice treated with mercuric chloride. Int Arch Allergy Immunol, **101**(4): 392-401.

Van-Zijverden M, van-der-Pijl A, van-Pinxteren F-A, de-Haar C, Penninks A-H, van-Loveren H, & Pieters R (2000) Diseal exhaust, carbon black, and silica particles display distinct Th1/Th2 modulating activity. Toxicol Appl Pharmacol, **168**: 131-139.

Varga J, Li L, & Jimenez S (1993) Increased type I collagen gene expression in L-tryptophan associated eosinophilia-myalgia syndrome skin fibroblasts. J Rheumatol, **20**: 1303-1308.

Varga J, Maul GG, & Jimenez SA (1992) Autoantibodies to nuclear Lamin C in the eosinophlia-myalgia syndrome associated with L-tryptophan ingestion. Arthritis Rheum, **35**: 106-109.

Verdier F, Virat M, & Descotes J (1990) Applicability of the popliteal lymph node assay in the Brown-Norway rat. Immunopharmacol Immunotoxicol, **12**(4): 669-677.

Vergani D & Mieli-Vergani G (2003) Autoimmune hepatitis. Autoimmunol Rev, **2**: 241-247.

Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, Chase HP, & Eisenbarth GS (1996) Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes, **45**: 926-933.

Vermeire S, Noman M, Van Assche G, Baert F, Van Steen K, Esters N, Joossens S, Bossuyt X, & Rutgeerts P (2003) Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. Gastroenterology, **125**: 32-39.

Vestergaard P (2002) Smoking and thyroid disorders--a meta-analysis. Eur J Endocrinol, **146**: 153-156.

Via CS, Shustov A, Rus V, Lang T, Nguyen P, & Finkelman FD (2001) *In vivo* neutralization of TNF-alpha promotes humoral autoimmunity by preventing the induction of CTL. J Immunol, **167**: 6821-6826.

Vial T, Choquet-Kastylevsky G, & Descotes J (2002) Adverse effects of immunotherapeutics involving the immune system. Toxicology, **174**(1): 3-11.

Vicario JL, Serrano-Rios M, San Andres F, & Arnaiz-Villena A (1982) HLA-DR3, DR4 increase in chronic stage of Spanish oil disease. Lancet, Jan 30;1(8266):276.

Vidali, M., Stewart, S. F., Rolla, R., Daly, A. K., Chen, Y., Mottaran, E., Jones, D. E. J., Leathart, J. B., Day, C. P. and Albano, E. (2003) Genetic and epigenetic factors in autoimmune reactions toward cytochrome P4502E1 in alcoholic liver disease. Hepatology 37, 410–419.

Viitala K, Makkonen K, Isreal Y, Lehtimaki T, Jaakkola O, Koivula T, Blake JE, & Niemela O (2000) Autoimmune responses against oxidant stress and acetaldehyde-dervied epitopes in human alcohol consumers. Alcohol Clin Exp Res, **24**: 1103-1109.

Villard-Mackintosh L & Vessey MP (1993) Oral contraceptives and reproductive factors in multiple sclerosis incidence. Contraception, **47**: 161-168.

Vimy MJ & Lorscheider FL (1990) Dental amalgam mercury daily dose estimated from intra-oral vapor measurements: a predictor of mercury accumulations in human tissues. J Trace Elem Exp Med, **3:** 111-123.

Vincent A, Palace J, & Hilton-Jones D (2001) Myasthenia gravis. Lancet, **357**: 2122-2128.

Vingerhoets AJ, Assies J, Goodkin K, Van Heck GL, & Bekker MH (1998) Prenatal diethylstilbestrol exposure and self-reported immune-related diseases. Eur J Obstet Gynecol Reprod Biol, **77**: 205-209.

Vinuya RZ, Canady AI, Wooley PH, Harrison DD, & Mitchell JA (1998) Immune reactions associated with sterile ventriculoperitoneal (VP) shunt malfunctions. J Allergy Clin Immunol, S76.

Vogel H (1999) Pathologic findings in nerve and muscle biopsies from 47 women with silicone breast implants. Neurology, **53**: 293-297.

Vogel A, Strassburg CP, Obermayer-Straub P, Brabant G, & Manns MP (2002) The genetic backgroud of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and its autoimmune disease components. J Mol Med, **80**: 201-211.

Vojdani A, Campbell A, & Brautbar N (1992) Immune functional impairment in patients with clinical abnormalities and silicone breast implants. Toxicol Ind Health, **8**: 415-429.

Vojdani A, Brautbar N, & Campbell AW (1994) Antibody to silicone and native macromolecules in women with silicone breast implants. Immunopharmacol Immunotoxicol, **16**: 497-523.

von Hertzen LC (2000) Puzzling associations between childhood infections and the later occurrence of asthma and atopy. Ann Med, **32**: 397-400.

Von Schmiedeberg S, Fritsche E, Ronnau AC, Specker C, Golka K, Richter-Hintz D, Schuppe HC, Lehmann P, Ruzicka T, Esser C, Abel J, & Gleichmann E (1999) Polymorphisms of the

xenobiotic-metabolizing enzymes CYP1A1 and NAT-2 in systemic sclerosis and lupus erythematosus. Adv Exp Med Biol, **455**: 147-152.

Vos JG (1986) Immunotoxicity of hexachlorobenzene. In: Morris CR & Cabral JR eds. Hexachlorobenzene: Proceedings of an international symposium. Lyon, International Agency for Research on Cancer, pp 347-356 (IARC Scientific Publications No. 77).

Vos J & Moore JA (1974) Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Int Arch Allergy Appl Immunol, **47**: 777-794.

Vos JG, Van Logten MJ, Kreeftenberg JG, & Kruizinga W (1979a) Hexachlorobenzene-induced stimulation of the humoral response in rats. Ann NY Acad Science, **320**: 535-550.

Vos JG, van Logten MJ, Kreeftenberg JG, Steerenberg PA, & Kruizinga W (1979b) Effect of hexachlorobenzene on the immune system of rats following combined pre- and postnatal exposure. Drug Chem Toxicol, **2**: 61-76.

Vos JG, Brouwer GMJ, Van Leeuwen FXR, & Wagenaar S (1983) Toxicity of hexachlorobenzene in the rat following combinede pre- and post-natal exposure: comparison of effects on immune system, liver and lung. Immunotoxicology, 219-235.

Vos JG, De Waal EJ, Van Loveren H, Albers R, & Pieters RHH (1999) Immunotoxicology. In: Nijkamp FP & Parnham MJ eds. Principles of Immunopharmacology. Basel, Birkhauser Verlag, pp 407-486.

Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, & Leonardo MJ (1999a) Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell, **98**: 47-58.

Wang JA, Fan S, Yuan RQ, Ma YX, Meng Q, Goldberg ID, & Rosen EM (1999b) Ultraviolet radiation down-regulates expression of the cell-cycle inhibitor p21WAF1/CIP1 in human cancer cells independently of p53. Int J Radiat Biol, **75**: 301-316.

Waterman SJ, El-Fawal HAN, & Snyder CA (1994) Lead alters the immunogenicity of two neural proteins: A potential mechanism for the progression of lead-induced neurotoxicity. Environ Health Perspect, **102**: 1052-1056.

Watts RA, Lane SE, Bentham G, & Scott DG (2000) Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum, **43**(2): 414-419.

Ways SC, Mortola JF, Zvaifler NJ, Weiss RJ, & Yen SSC (1987) Alterations in immune responsiveness in women exposed to diethylstilbestrol *in utero*. Fertil Steril, **48**: 193-197.

Weatherhill AR, Stang BV, O'Hara K, Koller LD, & Hall JA (2003) Investigating the onset of autoimmunity in As.W mice following treatment with 'toxic oils'. Toxicol Lett, **136**: 205-216.

Webb KB, Evans RG, Knudsen DP, & Roodman S (1989) Medical evaluation of subjects with known body levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. J Toxicol Environ Health, **28**: 183-193.

Weiner JA, Nylander M, & Berglund F (1990) Does mercury from amalgam restorations constitute a health hazard? Sci Total Environ, **99:** 1-22.

Weiss RA, Madaio MP, Tomaszewski JE, & Kelly CJ (1994) T cell reactive to an inducible heat shock protein induce disease in toxin-induced interstitial nephritis. J Exp Med, **180**: 2239-2250.

Weissman DN, Hubbs AF, Huang SH, Stanley CF, Rojanasakul Y, & Ma JK (2001) IgG subclass responses in experimental silicosis. J Environ Pathol Toxicol Oncol, **20**(Suppl 1): 67-74.

Wester L et al. (2003) Differential gene expression in pristane-induced arthritis susceptible DA versus resistant E3 rats. Arthritis Res Ther, **5**(6): R361-R372.

White KL Jr & Klykken PC (1998) The non-specific binding of immunoglobulins to silicone implant materials: the lack of a detectable silicone specific antibody. Immunol Invest, **27**: 221-235.

White KL, David DW, Butterworth LF, & Klykken PC (2000) Assessment of autoimmunity-inducing potential using the Brown Norway rat challenge model. Toxicol Lett, **112-113**: 443-451.

Whitekus MJ, Santini RP, Rosenspire AJ, & McCabe MJ Jr (1999) Protection against CD95-mediated apoptosis by inorganic mercury in jurkat T cells. J Immunol, **162**: 7162-7170.

Wichman I, Sanchez-Roman J, Morales J, Castillo MJ, Ocana C, & Nunez-Roldan A (1996) Antimyeloperoxidase antibodies in individuals with occupational exposure to silica. Ann Rheum Dis, **55**: 205-207.

Wick G, Brezinschek HP, Hala K et al. (1989) The obese strain of chickens: an animal model with spontaneous autoimmune thyroiditis. Adv Immunol , **47**: 433-500.

Williams DF (1996) Silicon, silicone, and silica: the importance of the right ending. Med Dev Techn, 7(1): 7-11.

Willis MS, Klassen LW, Tuma DJ, Sorrell MF, & Thiele GM (2002) Adduction of soluble proteins with malondialdehyde-acetaldehyde (MAA) induces antibody production and enhances T-cell proliferation. Alcohol Clin Exp Res, **26**: 94-106.

Willis MS, Thiele GM, Tuma DJ, & Klassen LW (2003) T cell proliferative responses to malondiadehyde-acetaldehyde haptenated protein are scavenger-receptor mediated. International Immunopharmacology **3**:1381–1399.

Willison HJ & Yuki N (2002) Peripheral neuropathies and anti-glycolipid antibodies. Brain, **125**: 2591-2625.

Wilson RH, McCormick WE, Tatum CF, & Creech JL (1967) Occupational acroosteolysis: Report of 31 cases. J Am Med Assoc, **201**: 577-581.

Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GR, Triplett DA, & Khamashta MA (1999a) International consensus

statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum, **42**: 1309-1311.

Wilson RB, Gluck OS, Tesser JRP, Rice JC, Meyer A, & Bridges AJ (1999b) Antipolymer antibody reactivity in a subset of patients with fibromyalgia correlates with severity. J Rheumatol, **26**: 402-407.

Winer JB (2001) Guillain Barre syndrome. Mol Pathol, **54**: 381-385.

Wingard DL & Turiel J (1988) Long-term effects of exposure to diethylstilbestrol. Western J Med, **149**: 551-554.

Winther JF, Bach FW, Friis S, Blot WJ, Mellemkjaer L, Kjoller K, Hogsted C, McLaughlin JK, & Olsen JH (1998) Neurologic disease among women with breast implants. Neurology, **50**: 951-955.

Winther JF, Friis S, Bach FW, Mellemkjaer L, Kjoller K, McLaughlin JK, Lipworth L, Blot WJ, & Olson JH (2001) Neurological disease among women with silicone breast implants in Denmark. Acta Neurol Scand, 103: 93-96.

Woeber KA (1991) Iodine and thyroid disease. Med Clin North Am, **75**: 169-178.

Wolf LE, Lappe M, Peterson RD, & Ezrailson EG (1993) Human immune response to polydimethylsiloxane (silicone): screening studies in a breast implant population. FASEB J, 7: 1265-1268.

Wong FS, Dittel BN, & Janeway CA Jr (1999) Transgenes and knockout mutations in animal models of type 1 diabetes and multiple sclerosis. Immunol Rev, **169**: 93-104.

Wooley PH, Griffin J, Panayi GS, Batchelor JR, Welsch KI, & Gibson TJ (1980) HLA-DR antigens and toxic reaction to sodium aurothiomalate and D-penicillamine in patients with rheumatoid arthritis. N Eng J Med, **303**: 300-302.

Wooley PH & Whalen JD (1991) Pristane-induced arthritis in mice. III. Lymphocyte phenotypic and functional abnormalities precede the development of pristane-induced arthritis. Cell Immunol, **138**(1): 251-259.

Wooley PH et al. (1998) Pristane-induced arthritis in mice: V. Susceptibility to pristane-induced arthritis is determined by the genetic regulation of the T cell repertoire. Arthritis Rheum, **41**(11): 2022-2031.

Woosley RL, Drayer DE, Reidenberg MM, Nies AS, Carr K, Oates JA (1978) Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. N Engl J Med, **298**: 1157-1159.

Wulferink M, Gonzalez J, Goebel C, & Gleichmann E (2001) T cells ignore aniline, a prohapten, but respond to its reactive metabolites generated by phagocytes: Possible implications for the pathogenesis of Toxic oil syndrome. Chem Res Toxicol, **14**(4): 389-397.

Xu D, Thiele GM, Beckenhauer JL, Klassen LW, Sorrell MF, & Tuma DJ (1998) Detection of circulating antibodies to maliondialdehyde-acetaldehyde adducts in ethanol-fed rats. Gastroenterology, **115**: 686-692.

Yamamoto K (2003) Pathogenesis of Sjogren's syndrome. Autoimmunol Rev, **2**: 13-18.

Yamauchi M, Maezawa Y, Mizuhara Y, Ohata M, Hirakawa J, Nakajima H, & Toda G (1995) Polymorphisms in alcohol metabolizing enzyme genes and alcoholic cirrhosis in Japanese patients: a multivariate analysis. Hepatology, **22**: 1136-11342.

Yang JM, Hildebrandt B, Luderschmidt C, & Pollard MK (2003) Human scleroderma sera contain autoantibodies to protein components specific to the U3 small nucleolar RNP complext. Arthritis Rheum, **48**(1): 210-217.

Yin M, Wheeler MD, Kono H, Bradford BU, Gallucci RM, Luster MI, & Thurman RG (1999) Essential role of tumor necrosis factor α in alcohol-induced liver injury in mice. Gastroenterology, **117**: 942-952.

Yee LJ, Kelleher P, Goldin R, Marshall S, Thomas HC, Alberti A, Chiaramonte M, Braconier J-H, Hall AJ, & Thursz MR (in press) Antinuclear antibodies in chronic hepatitis C virus infection: correlates of postivity and clinical relevance. J Viral Hepatitis.

Yen JH, Chen CJ, Tsai WC, Tsai JJ, Ou TT, & Liu HW (1999) HLA-DMA and HLA-DMB genotyping in patients with systemic lupus erythematosus. J Rheumatol, **26**: 1930-1933.

Yoo JH et al. (1999) Anticonvulsant hypersensitivity syndrome with an epoxide hydrolase defect. Br J Dermatol, **140**(1): 181-183.

Yoshida S, Gershwin ME. (1993) Autoimmunity and selected enviornmental factors of disease induction. Semin Arthritis Rheum, 22: 399-419.

Yoshino S (1994) Silicone induced arthritis in rats and possible role for T cells. Immunobiology, 192:40-47.

Yu J, Yu L, Bugawan TL, Erlich HA, Barriga K, Hoffman M, Rewers M, & Eisenbarth GS (2000) Transient antiislet autoantibodies: infrequent occurrence and lack of association with "genetic" risk factors. J Clin Endocrinol Metab, **85**: 2421-2428.

Yucesoy B, Vallyathan V, Landsittel DP, Simeonova P, & Luster MI (2002) Cytokine polymorphisms in silicosis and other pneumoconioses. Mol Cell Biochem, **234/235**(1-2): 219-224.

Yu-Lee LY, Luo G, Moutoussamy S, & Finidory J (1998) Prolactin and growth hormone signal transduction in lymphohemopoetic cells. Cell Mol Life Sci, **54**: 1067-1075.

Yung RL, Johnson KJ, & Richardson BC (1995) New concepts in the pathogenesis of drug-induced lupus. Lab Invest. **73**: 746-759.

Yung R, Powers D, Johnson K, Amento E, Carr D, Laing T, Yang J, Chang S, Hemati N, & Richardson B (1996) Mechanism of drug-induced lupus. II. T cells overexpressing lymphocyte function-associated antigen 1 become autoreactive and cause a lupuslike disease in syngenic mice. J Clin Invest, **97**(12): 2866-2871.

Yung R, Chang S, Hemati N, Johnson K, & Richardson B (1997) Mechanisms of drug-induced lupus. IV. Comparation of procainamide and hydralazine with analogs *in vitro* and *in vivo*. Arthritis Rheum, **40**(8): 1436-1443.

Yurino H, Ishikawa S, Sato T, Akadegawa K, Ito T, Ueha S, Inadera H, & Matsushima K (2004) Endocrine disruptors (environmental estrogens) e by B1 cells. Toxicol Sci, **81**:139-147.

Zandman-Goddard G, Blank M, Ehrenfeld M, Gilburd B, Peter J, & Schoenfeld Y (1999) A comparison of autoantibody production in asymptomatic and symptomatic women with silicone breast implants. J Rheumatol, 26: 73-77.

Zuniga R, Ng S, Peterson MGE, Reveille JD, Baethge BA, Alarcon GS, & Salmon JE (2001) Low-binding alleles of Fcγ receptor types IIA and IIIA are inherited independently and are associated with systemic lupus erythematosus in Hispanic patients. Arthritis Rheum, **44**: 361-367.

Zangrilli JG, Mayeno AN, Vining V, & Varga J (1995) 1,1'-Ethylidenebis[L-tryptophan], an impurity in L-tryptophan associated with eosinophilia-myalgia syndrome, stimulates type I collagen gene expression in human fibroblasts *in vitro*. Biochem Mol Biol Int, **37**: 925-933.

Zella JB & DeLuca HF (2003) Vitamin D and autoimmune diabetes. J Cell Biochem, **88**: 216-222.

Zenarola P, Gimma A, & Lomuto M (1995) Systemic contact dermatitis from thimerosal. Contact Dermatitis, **32**: 107-123.

Zhang SM, Willett WC, Hernan MA, Olek MJ, & Ascherio A (2000) Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol, **152**: 1056-1064.

Zhang SM, Hernán MA, Olek MJ, Spiegelman D, Willett WC, & Ascherio A (2001) Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. Neurology, **57**: 75-80.

Zheng Y & Monestier M (2003) Inhibitory signal override increases susceptibility to mercury-induced autoimmunity. J Immunol, **171**: 1596-1601.

Zhou Y, Gsicombe R, Huang D, & Lefvert AK (2002) Novel genetic association of Wegener's granulomatosis with the interleukin-10 gene. J Rheumatol, **29**: 317-320.

Zhou Y, Huang DR, Paris PL, Sauter CS, Prock KA, & Hoffman GS (2004) An analysis of CTLA-4 and proinflammatory cytokine genes in Wegener's granulomatosis. Arthritis Rheum, **50**: 2645-2650.

Ziegler AG, Hummel M, Schenker M, & Bonifacio E (1999) Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: the 2-year analysis of the German BABYDIAB Study. Diabetes, **48**: 460-468.