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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

**ENVIRONMENTAL HEALTH CRITERIA MONOGRAPH
ON PRINCIPLES AND METHODS FOR ASSESSING AUTOIMMUNITY
ASSOCIATED WITH EXPOSURE TO CHEMICALS**

PART 2: CHAPTERS 8 - 14

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8. NON-CHEMICAL FACTORS IN AUTOIMMUNITY

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 recurrence. 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.

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

3
 4 The weight of this evidence strongly suggests that rheumatic fever, and subsequent rheumatic
 5 heart disease, is an autoimmune disorder triggered by cross reactive proteins in particular strains
 6 of group A streptococci.

7

Autoimmune Disease	Possible infectious causes
Anti-phospholipid syndrome	Pneumonia, urinary tract infection, HCV, HIV
Behcet'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	Clostridium 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, Staphylococcus aureus

1 **8.1.2 *Hepatitis C virus.***

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

12
13 Autoimmune disease may be associated with these antibodies. Vasculitis is a well recognized
14 complication of persistent hepatitis C infection and is associated with cryoglobulinaemia. The
15 presence of anti-cardiolipin antibodies in association with clinical thrombosis has been reported
16 in these patients. The true incidence of these events has not been determined. Glomerulonephritis
17 is a well described association with HCV. These patients frequently have hypocomplementaemia
18 and circulating cryoglobulins. More controversial is a putative association with Sjogren's
19 syndrome with some authors claiming that 10-20% of patients may be affected and others
20 refuting this. Anti-Ro and anti-La antibodies do not appear to be markedly increased in HCV
21 infected subjects but there is a suggestion that sialoadenitis, occasionally with sicca symptoms
22 does occur at increased frequency. Similarly discrepant reports apply to the occurrence of
23 thyroid disease. Although it is clear that autoimmune thyroid disease is associated with the
24 interferon alpha therapy that many of these patients receive.

25
26 In summary autoantibodies are clearly increased in subjects with persistent HCV infection. The
27 true incidence of autoimmune diseases in comparison to an appropriate control group is yet to be
28 determined although there is good evidence to suggest that some associations do exist.

29
30 **8.1.3 *Multiple sclerosis***

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

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

14

15 **8.1.4 Immune programming**

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

29

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

1 **8.2 Vaccine-related factors**

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

4
5 **8.2.1 Vaccines themselves**

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

10

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

16

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

21

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

26

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

30

31 **8.2.2 Vaccine additives**

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

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

4
5 Alum is used as an adjuvant in several vaccines. It is a poor inducer of cell mediated immunity
6 and there is no evidence of it leading to autoimmunity.

7 8 **8.3 Dietary Factors**

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

22 23 **8.3.1 Caloric restriction and leptin**

24 The hormone leptin is produced by adipocytes and is involved in the regulation of food intake
25 and obesity. Periods of caloric restriction inhibit production of leptin. Fasting can improve
26 symptoms in some patients with rheumatoid arthritis (possibly through an anti-inflammatory
27 effect of fasting mediated through leptin), but the effects are not sustained when the fasting
28 period is over (Muller et al., 2001). In mouse models of multiple sclerosis (experimental
29 autoimmune encephalomyelitis) and type 1 diabetes, leptin secretion was closely linked to
30 disease onset (Sanna et al., 2003; Materese et al., 2002). Recent studies report an effect of leptin
31 on T cell stimulation and production of pro-inflammatory cytokines (Sanchez-Margalet et al.,
32 2003). Caloric restriction in lupus mouse models inhibits the disease process and prolongs
33 survival (Leiba et al., 2001).

34

1 **8.3.2 *Dietary fat and fatty acid content***

2 The type and amount of fat in foods is an important aspect of nutrition, with implications for
3 atherosclerosis, cardiovascular disease, and obesity as well as for immune-mediated diseases.
4 The fatty acid composition of foods is determined by the length of the carbon chain and the
5 number and location of double bonds. The “n-3” or “omega-3” fatty acids are those with one or
6 more double bonds, the first of which is located at the third carbon from the omega end of the
7 carbon chain. The essential fatty acids are those that can not be synthesized, and so are only
8 available from foods or supplements. Animal fats are a source of arachidonic acid (an omega-6
9 fatty acid) and fish is a source of the omega-3 fatty acids eicosapentaenoic acid (EPA) and
10 docosahexaenoic acid (DHA). EPA can also be converted from alpha-linoleic acid, found in
11 green leafy vegetables, flaxseed, and canola oils. Arachidonic acid and EPA are the specific
12 fatty acid precursors for the synthesis of specific prostaglandins (PGE) and leukotrienes (LTE).
13 The relative balance of different prostaglandins and leukotrienes affects the inflammatory
14 response. Arachidonic acid is converted to PGE₂ and LTE₄, which are pro-inflammatory,
15 stimulating natural killer cell activity and pro-inflammatory cytokines (e.g., interleukin-1 and
16 tumor necrosis factor- α). EPA is converted to the more anti-inflammatory compounds PGE₃
17 and LTE₅ (Calder, 1997; Simopoulos, 2002).

18
19 Because of the potential effects on inflammation and immune-mediated function, there has been
20 considerable interest in the potential therapeutic role of omega-3 fatty acids in autoimmune
21 disease. Most studies in humans have been among patients with rheumatoid arthritis. The
22 randomized clinical trials tend to be relatively small, but there is some evidence of improvement
23 in terms of reduced joint count and morning stiffness in trials of fish oil supplementation (Fortin
24 et al., 1995). There have also been some small trials ($n < 30$) of omega-3 supplementation in
25 patients with systemic lupus erythematosus, but these studies were conducted before the
26 adoption of standardized measures of disease activity and damage. In general, some
27 improvements in lipid profiles and inflammatory measures have been seen, but there are mixed
28 results with respect to improvements in clinic status. (Leiba et al., 2001). In a large
29 observational (non-randomized) study in Japan, there was no association between intake of total
30 fat, type of fat or omega 3 fatty acids and subsequent disease activity among 216 lupus patients
31 (Minami et al., 2003). In ulcerative colitis and Crohn’s disease, trials of omega-3 (fish oil)
32 supplements have reported improvements in terms of decreased steroid dosage, decreased
33 disease activity, prolonged periods of remission and increased weight gain, but there are

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

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

13 **8.3.3 Antioxidants**

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

26 **8.3.4 Vitamin D**

27 Vitamin D can be obtained from some foods, but its major source is through the action of
28 ultraviolet radiation which converts 7-dehydrocholesterol to cholecalciferol in the skin.
29 Hydroxylation of this compound in the liver produces 25-hydroxycholecalciferol [25-OHD₃],
30 which is then converted in the kidney to 1,25-hydroxycholecalciferol [1,25-(OH)₂D₃], the active
31 form of vitamin D. Vitamin D plays a major role in promoting absorption of calcium and
32 maintaining bone mineralization. Recently research has focused on immunosuppressive effects
33 of Vitamin D. The vitamin D receptor has been detected in lymphocytes and the thymus, and
34 vitamin D plays a role in T-cell mediated immune response (Deluca & Cantorna, 2001).

1

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

12

13 In murine models of experimental autoimmune encephalomyelitis (multiple sclerosis), type 1
14 diabetes, and inflammatory bowel disease, treatment with 1,25-(OH)₂D₃ (in conjunction with
15 adequate calcium intake) has been shown to inhibit the development of disease (Van Amerongen
16 et al., 2004; Hypponen, 2004; Froicu et al., 2003). In lupus mouse strains, however, a more
17 complex situation is seen, with some evidence of worsening of disease (particularly with respect
18 to measures of renal damage) with 1,25-(OH)₂D₃ treatment (Vaisberg et al., 2000).

19

20 **8.3.5 *L-Tryptophan***

21 Eosinophilia Myalgia Syndrome (EMS) is a multi-systemic, autoimmune disease that was first
22 diagnosed in 1989 and was associated with the use of contaminated L-tryptophan (Hertzman et
23 al., 1990). An essential amino acid and serotonin precursor, L-tryptophan is used to treat
24 depression, premenstrual syndrome, and insomnia. In nine months, 1658 people were diagnosed
25 with the disease in the United States, Germany and Belgium (Swygert et al., 1990; Andre et al.,
26 1991; Carr et al., 1994). A product recall dramatically reduced the number of new cases
27 reported, although approximately 3% of EMS patients did not use L-tryptophan (Swygert et al.,
28 1990). Rare non-L-tryptophan-associated cases continue to be reported (Margolin, 2003).

29 Although EMS was most frequently reported in women (84%), non-Hispanic whites (97%), and
30 residents of western states (Swygert et al., 1990), statistical analysis showed no correlation with
31 duration of L-tryptophan intake, concurrent medications (Kamb et al., 1992; Carr et al., 1994;
32 Kaufman & Krupp, 1995), gender or race, since the majority of people using these products are
33 female (60%) and white (80%). There have been associations with dose, age of the patient
34 (average 48 years), and a single supplier that had made changes in the manufacturing process

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

9
10 Gene expression and protein synthesis of fascial TGF-1 β , fibronectin, and Type IV collagen
11 (Peltonen et al., 1991), and fibroblast Type I collagen (Varga et al., 1993; Hitraya et al., 1997)
12 from human EMS affected tissue and cells were increased, compared to controls. These reports
13 suggest that the cytokine TGF-1 β , upregulation of collagen genes, and subsequent accumulation
14 of collagen, may play a role in the development of connective tissue alterations, especially
15 diffuse fasciitis and cutaneous fibrosis (Peltonen et al., 1991; Varga et al., 1993). Muscle and
16 fascia from EMS patients revealed an inflammatory exudate composed primarily of activated T
17 cells and macrophages at perimysial, endomysial, perivascular, and fascial sites. CD8⁺ cells
18 were the dominant T-cell subpopulation and MHC class I antigen complex expression was
19 increased on inflammatory and endothelial cells and muscle fibers, indicating a cell mediated
20 immune response targeting connective tissue. Emslie-Smith, et al. (1991) proposed that a
21 contaminant of L-tryptophan haptenates a connective tissue component, forming a stable,
22 immunogenic complex and initiating an autoimmune response that is augmented by the local
23 release of inflammatory cytokines from activated cells, however the specific cellular target is not
24 yet known.

25
26 A higher incidence of mutation in the cytochrome P450 CYP2D6 gene, resulting in the poor
27 metabolizer genotype, and the absence of activity in the corresponding enzyme among EMS
28 cases (n=27) indicate that altered xenobiotic metabolism may play a role in the pathogenesis of
29 EMS (Flockhart et al., 1994). Animal models also suggest a genetic component to EMS
30 susceptibility; autoimmune-prone NZBWF1 mice and Lewis rats have a lower hepatic nuclei
31 binding affinity for case-associated L-tryptophan compared to Swiss mice and Sprague-Dawley
32 rats, respectively (Sidransky and Verney, 1994; Sidransky and Verney, 1997). Two
33 contaminants identified in the tryptophan preparations associated with EMS, 1,1'-
34 Ethylidenebis[L-tryptophan] (EBT) and 3-(phenylamino)-L-alanine (PAA), have been the focus

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

16

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
AU-salts
D-Penicillamine
Nevirapine

{	IC-glomerulonephritis
	Skin pathology; dermatitis
	Polyclonal IgE
	AutoAb (Type IV-collagen, ANA, anti-ACh, anti-thyroglobulin)
	Systemic inflammatory response with autoimmune symptoms

HCB*

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-fibrillar
	anti-insulin

C57BL/Ks

STZ

Type 1 Diabetes

DBA/1 susceptible
DBA/2 resistant
Neonatal mouse

Pristane

Pristane induced arthritis

CsA

Multi-organ type
inflammation***Cat***

6-propylthiouracil

SLE: ANA, Sm antigen
lymphadenopathy, hemolytic
anemia***Dog***Beagle
DobbermanProcainamide
Sulfonamides
Radiocontrast media
Etoposide

{	ANA
	Multiples symptoms including skin eruptions (urticaria) and blood dyscrasias

Chickens

OS

Iodine

Autoimmune thyroiditis

MonkeyL-canavanine
(alfa-alfa seeds)

SLE, ANA

see text for more information and references

1 **9.2 Rat models**

2 **9.2.1 The Brown Norway rat model**

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

7
8 Qasim et al., 1997), hexachlorobenzene (HCB) (Michielsen et al., 1999; Ezendam et al., 2004a;
9 Ezendam et al., 2004b; Vos et al., 1979a) and recently nevirapine (Shenton et al., 2003) have
10 been shown to induce clinical effects. Captopril (Donker et al., 1984) and also felbamate
11 (Popovic et al., 2004) were tested in BN rats as well but, appeared to be ineffective.

12
13 Effects that are reported are only partly compound-specific and include both organ-specific
14 effects (glomerulonephritis, splenomegaly, skin rashes) and systemic effects
15 (hyperimmunoglobulinemia, in particular IgE, and increased levels of autoantibodies).

16 Derangements in BN are accompanied by polyclonal lymphoproliferation (both T and B cells)
17 (Hirsch et al., 1986; Hirsch et al., 1982).

18
19 BN rats are known as so-called Th2-prone animals (e.g. they are activated to produced high
20 levels of IgE and to display many characteristics of type 2 immune response). This property
21 and/or the underlying genetic trait may be responsible for the high susceptibility of this strain to
22 chemical-induced autoimmune effects and is often brought forward as a drawback of using this
23 strain. But again, as for disease-prone mouse strains, it can also be argued that the inherent
24 susceptibility of this rat strain resembles the inherent susceptibility in human cases of chemical-
25 induced autoimmune disorders.

26 27 **9.2.1.1 Metals**

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

1 autoimmunity. These phenomena, transience of autoimmune effects as well as low-dose
2 protection, is shown to be due at least in part to the development of regulatory immune cells. In
3 case of HgCl₂, these cells have been identified as either IFN- γ -producing CD8⁺CD45RChigh
4 regulatory T cells (Pelletier et al., 1990; Szeto et al., 1997; Mathieson et al., 1991; Field et al.,
5 2003) or RT6.2⁺ T cells (Kosuda et al., 1994). In view of this, it is relevant to note that Lewis
6 rats which produce predominantly CD8⁺ regulatory T cells ('suppressor' T cells) in response to
7 HgCl₂, are resistant to HgCl₂-induced autoimmunity, and rather display a polyclonal
8 immunosuppressive response (Pelletier et al., 1987). Concordingly with this strain sensitivity, it
9 has been clearly demonstrated that susceptibility to HgCl₂ induced autoimmune effects are
10 dependent on MHC-II haplotyp (Aten et al., 1991).

11

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

15

16 *9.2.1.2. D-Penicillamine*

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

26

27 *9.2.1.3 Hexachlorobenzene*

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

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

6 7 *9.2.1.4 Nevirapine*

8 Nevirapine is used to treat HIV-infected patients, and in some individuals this drug causes severe
9 skin rash. Similarly, nevirapine has been found to cause skin rash in 100% of high-exposed (150
10 mg/kg) female BN rats (Shenton et al., 2003). Female Sprague Dawley rats were less sensitive
11 (21% of rats showed a rash), and male BN or Sprague Dawley rats, and female Lewis rats were
12 resistant. Low dose pretreatment with nevirapine also (similar to D-penicillamine and HgCl₂)
13 induced tolerance to subsequent normal high doses and upon transfer of splenocytes from sick to
14 naive animals nevirapine-induced rash occurred earlier. In addition, upon rechallenge with
15 nevirapine the rash developed faster in previously exposed but fully recuperated rats. In all
16 nevirapine-induced disease in BN rats is clearly immune-mediated (Shenton et al., 2003).

17 18 **9.2.2 Other rat models**

19 *9.2.2.1 Cyclosporin A-induced Autoimmunity (CsA-AI)*

20 Cyclosporin (CsA) is able to induce an autoimmune syndrome in Lewis rats, but only when these
21 rats are subjected to lethal (8.5 Gy X irradiation) and reconstituted with syngeneic or autologous
22 bone marrow (Damoiseaux, 2002). About two weeks after cessation of CsA treatment, which
23 starts on the day of the bone marrow transplantation, the rats start to develop autoimmune
24 disease. Acute symptoms of CsA-induced Autoimmunity (CsA-AI) is similar to GvHD, with
25 erythroderma, dermatitis and alopecia and the chronic phase is characterized by progressive
26 alopecia combined with scleroderma-like skin pathology. CsA-AI is clearly immune dependent
27 and involves autoreactive T cells (specific for MHC class II-paptied named CLIP) and requires
28 both an intact thymus and absence of a regulatory T cells (CD45R^{low}CD4⁺ phenotype)
29 (Barendrecht et al., 2002). The effect of CsA on the thymus has been subject of many studies and
30 it turned out that CsA inhibits differentiation of CD4⁺CD8⁺ thymocytes possibly by interference
31 with activation-induced cell death (Shi et al., 1989). This probably is the cause of the increased
32 release of auto-reactive T cells (Kosugi et al., 1989). In line with this and with the protocol
33 required to induce CsA-AI in rat, neonatal administration of CsA in mice also induces a
34 multiorgan-type autoimmune disease (Sakaguchi & Sakaguchi, 1989).

1 **9.3 Mouse models**

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

6 **9.3.1 Metals**

7 Subcutaneous administration of HgCl₂ (Mirtcheva et al., 1989; Kubicka-Muranyi et al., 1995;
8 Kubicka-Muranyi et al., 1996) or intramuscular treatment with Au(I)-salts (Schuhmann et al.,
9 1990) has been shown to induce anti-nuclear and anti-nucleolar autoantibodies (ANA, AnolA)
10 from around 4 weeks of exposure in particular in high responding A.SW mice (MHC-H2s
11 haplotype). Other H2s mice, such as B10s mice are also susceptible, but congenic H2d mice (e.g.
12 B10D2) or H2k mice (B10.BR) are resistant to HgCl₂-induced autoimmune effects, indicating the
13 importance of MHC haplotype (Mirtcheva et al., 1989). The response to HgCl₂ in A.SW mice is
14 Th2 mediated, involving IL-4 production and increases in IgE and IgG1 levels (Ochel et al., 1991).
15 Interestingly, both H2s and H2d mice responded to HgCl₂ exposure with an increase in the number
16 of activated CD4⁺CD45R^{low} effector T cells (van Vliet et al., 1991), implying that the difference
17 between these strains also involves immunoregulatory processes HgCl₂ given orally via the
18 drinking water also induced antinucleolar antibodies (IgG-class) in SJL/N (H2s) mice after 10
19 weeks (Hultman & Enestrom, 1992).

21 **9.3.2 Drugs**

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

24
25 D-penicillamine has been shown to induce anti-ssDNA and anti-insulin antibodies in C57BL/Ks
26 (H2d) and C3H/He (H2k) but not in BALB/c or C57BL/6 mice after subcutaneous exposure for 4
27 weeks (Brik et al., 1995). Also after oral treatment (for 7 to 8 months, in the drinking water) D-
28 penicillamine (and in the same study also quinidine) induced an increase in auto-antibodies in
29 A.SW/Sn (H2s) mice (Monestier et al., 1994).

30
31 The anti-neoplastic drug streptozotocin (STZ) is capable of inducing immune-dependent diabetes
32 mellitus (IDDM) when administered (intraperitoneally) at low dose on 6 consecutive days.
33 Important to note is that a strong dependency on strain and/or gender has been observed, being
34 male C57BL/Ks (H2d) mice most sensitive (Leiter, 1982; Herold et al., 1996). Unlike most other

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

4
5 Procainamide has been found to induce an increase in ANA in A/J mice after 8 months of exposure
6 via the drinking water (Layland et al., 2004). This increase appeared mediated by CD25-CD4⁺ T
7 cells and regulated by CD25⁺CD4⁺ regulatory T cells.

8
9 Diphenylhydantoin (via drinking water for 6 months) was tested in genetically predisposed mice
10 (C57BL/6-lpr/lpr strain) but the compound was rather depressed levels of autoantibodies (Bloksma
11 et al., 1994), (*see also part 4.1?*). In another study (Okada et al., 2001), a slight shift towards a Th2
12 response was demonstrated by showing an increase in the KLH-induced production of IL-4 and IgE
13 (IgE was detected by direct ELISA, which makes these data doubtful) in a 4 weeks exposure study.
14 However, in this study spleen proliferation responses were also suppressed, and Robinson et al.
15 (1986) have compared in one study a large number of MHC-defined mouse strains with respect to
16 induction of antinuclear autoantibodies by HgCl₂ (*subcutaneously*, detected after 0.5 to 2 months),
17 gold salts (*intramuscularly*, detected after 1 to 5 months) and D-penicillamine (*orally*, detected
18 after 4.5 to 5 months) and reported that A.SW mice were high responders to all three chemicals.

20 **9.3.3 Pristane**

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

29
30 PIA is also inducible in rat, with DA rats being susceptible and E3 rats being resistant (Wester et
31 al., 2003), and controlled by multiple genes, identified as Pia loci (Olofsson et al., 2003).

32 **9.4. Genetically predisposed animal models**

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

8 In induced models, a susceptible animal strain is immunized with a mixture of an adjuvant and
9 an autoantigen isolated from the target organ. Examples are adjuvant arthritis (AA) (Pearson,
10 1956), and experimental allergic encephalomyelitis (EAE) (Ben-Nun & Cohen, 1982) in the
11 Lewis strain rat. Examples of spontaneous models of autoimmune disease are the BB-rat
12 (Mordes et al., 1987; Prins et al., 1991) and the NOD-mouse (McDevitt et al., 1996) that develop
13 autoimmune pancreatitis and subsequently diabetes, or the (NZBxNZW)F₁ or MRL/lpr mouse
14 (Pollard et al., 1999; Shaheen et al., 1999) that spontaneously develop systemic lupus
15 erythematosus (SLE)-like disease.

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

20

21 **9.4.1 SLE-prone strains of mice**

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

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

3

4 **9.5 Other species**

5 **9.5.1 Dogs**

6 Dogs is a species frequently used in toxicity studies. However, there are only few reports in open
7 literature on dog studies with respect to chemical- or drug-induced hypersensitivity reactions or
8 autoimmune effects, and studies are also often contradicting. For instance, procainamide has
9 been shown to induce lupus like symptoms (mainly increase of antinuclear antibodies) in one
10 study (Balazs & Robinson, 1999), but not in another study with younger dogs (Dubois & Strain,
11 1972). Similar discrepancies were observed for hydralazine-induced effects in dogs (Kammuller
12 et al., 1989).

13

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

20

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

25

26 **9.5.2 Miscellaneous**

27 Apart from the species mentioned, other species used to study chemical induced autoimmune
28 phenomena or systemic hypersensitivity reactions. Experiments (Aucoin, 1989) with cats
29 showed that propylthiouracil (PTU) induces SLE-like phenomena (autoantibodies against
30 nuclear antigen, Smith (Sm) antigen, red blood cells and cytoplasmic components,
31 lymphadenopathy, weight loss). However, important PTU-induced symptoms, like
32 agranulocytosis and liver toxicity, observed in man are not observed in cat (Shenton et al.,
33 2004). In addition, the finding that symptoms after rechallenge occur with the same delay in
34 time are not supportive for an immunological nature of the phenomena in cat. The model could

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

3
4 Chemical (incl. diet mediated)-induced autoimmune effects in other species have also been
5 documented, but in most if not all cases, they are limited to isolated cases (for review see Kosuda
6 & Bigazzi, 1996). For instance, Monkeys fed alfalfa-seeds developed antibody-induced anemia,
7 chickens (Cornell C strain) receiving excess of iodine developed antibodies against thyroid
8 hormones and lymphocytic thyroiditis, halothane-treated rabbits displayed antibodies against a
9 set of 5 endogenous antigens and drug-specific antibodies to a number of drugs (including
10 isoniazid and procainamide) were detected in Guinea pigs (upon injection of drug in combination
11 with CFA) (Aida et al., 1998; Katsutani & Shionoya, 1992). With regard to the Guinea pig
12 however, it appeared recently based of FDA records that this species does not provide a reliable
13 predictive animal model (Hastings, 2001).

15 **9.6 Local lymph node assays**

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

20
21 In particular the PLNA has been extensively used to evaluate the potential of certain drugs to
22 stimulate the immune system, and when proper immunologically relevant parameters are
23 assessed the PLNA may also identify immunosensitizing potential (Pieters & Albers, 1999)..

24
25 The PLNA is mostly performed in mice (Gleichmann, 1981; Bloksma et al., 1985; Goebel et al.,
26 1996) but also rats (Verdier et al., 1990; Descotes, 1992) have been used basically determines
27 changes in the paw-draining lymph node upon subcutaneous injection of a suspected chemical
28 into footpad. The response, which can be assessed by detecting lymphocyte proliferation, but
29 also by detecting changes in the distribution leukocyte subsets, cytokine production or
30 immunohistology, is determined 6 to 8 days after injection.

31
32 Recent modifications include the use of reporter antigens, hence the reporter-antigen PLNA or
33 RA-PLNA (Albers et al., 1997; Gutting et al., 2002a). RA can be regarded as bystander antigens
34 and the response to RA can be determined fairly easily by ELISPOT-assay. Depending on the

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

12
13 Up till now, 130-140 compounds (Kammuller et al., 1989b; Albers et al., 1997; Shinkai et al.,
14 1999; Pieters & Albers, 1999; Gutting et al., 1999; Gutting et al., 2002a) including a substantial
15 number of structural homologues of diphenylhydantoin (Kammuller & Seinen, 1988) and
16 zimeldine (Thomas et al., 1989; Thomas et al., 1990), have been tested in the PLNA, and those
17 chemicals with known immunostimulating activity in man were out correctly. However,
18 compounds that require metabolic conversion turned out to be false negative unless metabolic
19 systems (myelin peroxidase (MPO) positive phagocytes, S9 mix) were added as well.

20
21 Recently, an inventory study was carried out to evaluate the predictive value of local lymph node
22 approach for the immunosensitizing potential of drugs. Since the footpad injection raises ethical
23 concerns in some instances head-injection and ear-injection with the auricular lymph node as
24 read-out organ were used instead. The head injection protocol showed that of ## the drugs tested
25 were positive and that compounds that were negative mostly were known to require metabolic
26 activation. In a study using the RA-protocol with TNP-Ficoll as RA, ear-injection and
27 subsequent detection of specific antibody formation with a range of pharmaceuticals showed
28 comparable results with the RA-PLNA (Nierkens et al., 2004).

29
30 The major drawback route of the PLNA and other local lymph node approaches for drug testing
31 is the route of exposure as most drugs are taken orally. However, the RA approach may also be
32 applicable in combination with oral exposures. It appeared that oral exposure to D-penicillamine,
33 diclofenac or nevirapine for variable periods of time stimulated the DTH and/or antibody

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

3
4 In addition, single oral exposures of D-penicillamine (Nierkens et al, 2005, in press) or
5 diclofenac (Gutting et al., 2002b); Nierkens et al, in press) have also been shown to cause
6 chemical specific T cell sensitization. This sensitization could be detected as an increased IgG1
7 response to TNP-Ficoll in the PLN after challenge of TNP-Ficoll together with subsensitizing
8 doses of the respective drugs in the paw.

9

10 **9.7 Concluding remarks**

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

18

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

31

32

33

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

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

19

20 ***10.2.2 Counter-immuno electrophoresis***

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

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

7 **10.2.3 Haem-agglutination**

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

32 **10.2.4 Enzyme-linked immuno-sorbent assay/fluorescent enzyme immuno-assay**

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

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

31

32 ***10.2.5 Radio-immuno assay***

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

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

10

11 ***10.2.6 Immunoblotting***

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

31

32 ***10.2.7 Multiplex analysis***

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

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

14

15 **10.3 Selection of detection method**

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

26

27 **10.3.1 Autoantigens**

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

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

23

24 **10.3.2 Anti-immunoglobulin reagents**

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

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

24

25 **10.4 Clinical interpretation**

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

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

10
11 It is of great practical concern to know the predictive value of positive and negative test results,
12 that is the proportion of those with a positive test who actually have the disease, and the
13 proportion of those with a negative test who actually do not have the disease, respectively
14 (Box 1). These values strongly depend on the true prevalence of the disease under study.
15 Likelihood ratios (LRs), on the other hand, indicate the proportion of individuals with and
16 without the disorder at a given level of a diagnostic test (Box 1). Since the LRs are calculated as
17 a ratio of probabilities, they are not influenced by disease prevalence. Furthermore, LRs can be
18 used in a Bayesian context to generate a post-test probability of disease. Finally, it is important
19 to realize that the variability of the reported values for test systems can differ because a variable
20 amount of healthy controls, and/or relevant disease controls are included in the different studies.
21 Therefore, values given in the literature or by the manufacturer of commercial kits should be
22 interpreted in this context and all laboratories should be recommended to determine their own
23 test characteristics.

24
25 Two other test parameters that are important for interpretation of results are the intra- and inter-
26 assay variation. These parameters give information on the reproducibility and reliability of the
27 results. The intra-assay variation is determined by running multiple preparations (5 or more)
28 from the same test sample in the same assay. The intra-assay variation can be calculated as the
29 ratio of the standard deviation and the mean, and is expressed as percentage after multiplying
30
31 the ratio by 100. The inter-assay variation is determined by running the same test sample in
32 multiple, consecutive assays (5 or more). The formula for calculating the inter-assay variation is
33 similar to the one for calculating the intra-assay variation. Preferentially these variations are
34 determined in samples with low, medium, and high values. In general the inter-assay variation is

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

4
5

Box 1: Formulae of test parameters

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

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

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

Positive predictive value = $\frac{\text{true positive}}{\text{true positive} + \text{false positive}} = \frac{A}{A + B}$
 = $\frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}$

Negative predictive value = $\frac{\text{true negative}}{\text{false negative} + \text{true negative}} = \frac{D}{C + D}$
 = $\frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}$

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

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

6
7

1 **10.5 Human immunoglobulins**

2 *10.5.1 Autoimmune disease and human immunoglobulin levels*

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

27

28 *10.5.2 Quantification of human immunoglobulins*

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

1 IgD and IgE are much lower (IgD: 0.04 g/L; IgE: 3×10^{-5} g/L), more sensitive assay methods are
2 required for the detection of these latter two isotypes.

3
4 Nephelometry and turbidimetry are based on the formation of immune complexes in solution and
5 the subsequent effect on light scattering of incident light. The basic principles of light scattering
6 by particles is beyond the scope of this discussion. The formation of immune complexes is
7 accomplished by the addition of an optimised dilution of specific antiserum to a dilute antigen
8 solution resulting in more or less equivalent presence of antigen and antibody. As already stated,
9 immune complex formation is prevented in situations of antigen excess or antibody excess. The
10 newly formed immune complexes will scatter light from an incident light beam. In case of
11 nephelometry increased side scattering at an angle to the incident light beam is determined, while
12 in case of turbidimetry the loss in light intensity passing straight forward through the solution,
13 due to side scattering, is measured. Some automates combine both detection principles for
14 calculating antigen concentrations. As mentioned above, these techniques are very suitable for
15 quantifying the immunoglobulin isotypes IgA, IgG, and IgM. The IgG subclasses, in particular
16 IgG3 and IgG4, are present in the circulation in relatively low concentrations. They can be
17 quantified by nephelometry/turbidimetry if the immune complex formation is enhanced. This is
18 achieved by coupling the specific antiserum to, for instance, latex particles. In any case,
19 quantitative results are obtained by relating the signal of the test sample to calibrators that have
20 assigned values for the antigen of interest.

21
22 The radial immuno diffusion (RID) or Mancini assay is also based on the formation of immune
23 complexes. This occurs in an agarose matrix containing the specific antiserum. The antigen is
24 applied into a small hole in the matrix and disperses through this matrix due to diffusion. As
25 soon as equivalent concentrations of antigen and antibody are reached, the molecules will
26 precipitate revealing a precipitin ring. There is a linear relationship between the antigen
27 concentration and the squares of the ring diameters (endpoint method), or between the log of the
28 antigen concentration and the ring diameters (timed-diffusion method). The use of appropriate
29 calibrators enables quantification of results. This technique is often applied for the detection of
30 IgG subclasses and IgD concentrations.

31
32 Finally, the extremely low IgE concentration in the circulation requires very sensitive detection
33 methods, i.e. ELISA/FEIA, RIA, or modifications of these methods. Basically, these techniques
34 are similar as described for the detection of autoantibodies. In case of ELISA/FEIA it concerns a

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

5 **10.6 Testing in the diagnosis of delayed-type chemical hypersensitivity**

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

15 Skin testing is based on the application of chemical solutions on the epidermis, with (scratch-
16 patch test) or without (patch test) scarification of the epidermis. The occurrence of a typical type
17 IV hypersensitivity reaction, i.e. erythema, vesiculation, and evidence of cellular infiltrate, 48 to
18 96 hours after application is typical for a positive reaction. Topical chemical application, usually
19 on the upper and mid zone of the back, is performed to avoid the risks of systemic rechallenge. A
20 drawback of this approach is that the metabolism of the chemical, leading to the generation of a
21 reactive metabolite, and the presentation of the chemical to the immune system may be different
22 according to the route of entry. Other limitations to the interpretation of *in vivo* tests are that co-
23 factors of critical importance may be absent when the test is performed or that the test may be
24 performed too early after the adverse chemical reaction while the immune system may still be in
25 a refractory state. It is therefore recommended to perform skin tests within 6-12 weeks after the
26 occurrence of the adverse chemical reaction.

27
28 *In vitro* testing of delayed-type chemical hypersensitivity is based on the detection of chemical-
29 specific IgG antibodies and/or T-cells. chemical-specific IgG antibodies are detected in solid
30 phase assays where the chemical is bound to various carriers like nitrocellulose or sepharose.
31 These methods are controversial and are not recommended for the routine diagnosis of chemical
32 hypersensitivity. Chemical-specific T-cell responses are measured in the so-called LTT. This test
33 reveals a sensitisation of T-cells by an enhanced proliferative response of peripheral blood
34 mononuclear cells to a certain chemical. Generally, lymphocyte transformation is measured by

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

6
7 Altogether, accurate and reliable diagnostic tests for the evaluation of adverse chemical reactions
8 remain problematic. At the present time, none of these tests has been properly validated as a
9 specific and sensitive diagnostic tool of delayed-type chemical hypersensitivity. Moreover, these
10 tests only enable immune reactivity to the chemical itself: in cases where the chemical elicits an
11 immune reaction to autologous antigens, conventional methods for the diagnosis of autoimmune
12 diseases, as discussed in the first part of this chapter, are more appropriate. Table 14 lists a broad
13 panel of laboratory tests (general and immunological) to enable detection of a variety of
14 abnormalities associated with induction of autoimmunity that may occur after environmental
15 chemical exposure. Obviously, this screening panel should be done in conjunction with clinical
16 evaluation since positive results in laboratory testing do not make a diagnosis or predict the
17 subsequent development of autoimmune disease. Further, more specific testing should be done to
18 aid in the diagnosis of possible autoimmune disease.

20 **10.7 Conclusions**

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

1 Registry include anti-nuclear antibodies, rheumatoid factor, and anti-thyroglobulin antibodies,
2 whereas the United States National Academy of Sciences recommended beside the tests
3 suggested by the WHO, also antibodies to red blood cells. However, no advice with regard to
4 the method of detecting these autoantibodies and relevant cut-off values are given and, as stated
5 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.
- Urinalysis (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.

1 **List of abbreviations**

2

3	CIE	counter-immuno electrophoresis
4	ds	double-stranded
5	ELISA	enzyme-linked immunosorbent assay
6	ENA	extractable nuclear antigens
7	FEIA	fluorescent-enzyme immuno-assay
8	FITC	fluorescein isothiocyanate
9	IIF	indirect immunofluorescence
10	LR	likelihood ratio
11	LTT	lymphocyte transformation test
12	RIA	radio-immuno assay
13	RID	radial immuno diffusion
14	ROC	receiver operating characteristics
15	WHO	World Health Organization

1 **11. RISK ASSESSMENT**

2

3 **11.1 Introduction**

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

16

17 **11.2 Prevalence of autoimmune diseases**

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

30

31 **11.3 Immune mechanisms**

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

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

20
21 Immune responses are often categorized according to Gell and Coombs' classification. This
22 categorization into four classical types of hypersensitivity responses does however not hold any
23 longer with regard to drug-induced allergic and autoimmune-like phenomena. For instance with
24 regard to Type IV delayed type hypersensitivity reactions, a revision has been proposed to
25 include other T cell mediated clinical symptoms such as exanthema with eosinophilia. In
26 addition some drugs may induce adverse immune effects without immunosensitization, these
27 immune effects are collectively designated as pseudo-allergic reactions. Also, one drug often
28 elicits a wide range of systemic pathological effects that can be linked to more than one of the
29 four classical types of hypersensitivity responses. The fact that certain chemicals induce a variety
30 of hypersensitivity reactions may indicate that they affect the immune system at more than one
31 particular stage, which has important implications for understanding the mechanisms.

32

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

^a from: Luster et al (1999)

1 **11.5 Animal models to assess chemical induced autoimmunity**

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

10

11 ***11.5.1 Dose-regimen and immunoregulation***

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

18

19 ***11.5.2 Genetics and immunoregulation***

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

27

28 **11.6 Induced and genetic models**

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

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

8

9 **11.7 Predictive models for autoimmunity and hypersensitivity**

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

15

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

21

22 ***11.7.1 Primary PLNA and secondary and adoptive PLNA***

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

34

1 **11.7.2 Reporter antigen PLNA**

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

16
17 Presently, around 130 compounds have been tested, predominantly in the primary PLNA (Pieters
18 & Albers, 1999}. For those chemicals with known adverse immune effects PLN-responses show a
19 good correlation with the reported ability of a compound to induce AID or contact dermatitis in
20 man. Importantly, if metabolism is considered no false negatives are found. Thus, the direct
21 PLNA seems to be a versatile tool to recognize T-cell activating drugs and chemicals, including
22 autoimmunogenic chemicals, keeping in mind possible false-negative results with prohaptens.

23
24 Interestingly, the PLNA technique can be used in combination with relevant route of exposure
25 models. Basically, local assessment of T cell activation in the popliteal lymph node in response
26 to a subcutaneously injected non-immunogenic dose of an appropriate chemical (a hapten,
27 relevant metabolite, native autoantigen or a reporter antigen) may assess the presence of
28 systemic T cell memory and hence systemic immunosensitization in animals that have been
29 exposed to the chemical for a certain period. For example, by combining oral exposure to
30 diclofenac with the RA-PLNA with TNP-Ficoll as read-out method Gutting et al. (2002b)
31 reported that a single oral dose of diclofenac resulted in an increased IgG1 response to TNP-
32 Ficoll when co-injected in the paw with a non-sensitizing dose of the drug, indicating that oral
33 exposure to the diclofenac causes compound-specific T cell memory.

1 **11.8 Testing strategy**

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

9
10 In the second tier, chemicals that are positive in the PLNA should then be examined in suitable
11 animal models that use systemic exposure routes (mostly oral) and clinical outcome to further
12 assess autoimmunogenic potential. In this, high priority has to be given to the validation of the
13 PLNA and the further development of predictive animal assays. It is important to note that the
14 PLNA in any of its forms is a hazard identification test and belongs to the qualitative stage of the
15 risk assessment paradigm. Because of the lack of suitable and validated animal models, including
16 models to quantify acceptable levels of exposure, the potential risk for inducing autoimmunity
17 cannot be predicted at present. As regulatory guidance is following science, such guidance for
18 autoimmunity is not available.

19
20

1 **12 CONCLUSIONS AND RECOMMENDATIONS**

2
3 **Conclusions**

- 4
- 5 1. Autoimmune diseases are an important health problem, affecting 3-5% of the population.
6 Furthermore, autoimmune mechanisms play a role in many other diseases, hence more
7 than these 3-5% will encounter autoimmune-associated health effects.
8
- 9 2. The information yielded by epidemiology studies pertaining to chemical-induced
10 autoimmunity are hampered because of problems in designing and standardizing such
11 studies. The current figures on prevalence may actually be underestimated. There is
12 epidemiological evidence of increasing prevalence of AID in the Western countries,
13 which cannot be attributed to better diagnostics alone.
14
- 15 3. Autoimmunity and autoimmune diseases consequences of multifactorial phenomena. The
16 various mechanisms of interactions of endogenous and environmental factors with the
17 immune system leading to autoimmune diseases are reviewed in this monograph. In
18 addition to genetic factors, exogenous factors include infections, components in food,
19 drugs and environmental chemicals.
20
- 21 4. Of the environmental factors, drug-induced autoimmune disorders and hypersensitivity
22 reactions are a major concern, and often the reason for withdrawing drugs from the
23 market or restricting their use.
24
- 25 5. In contrast to the great variety of methods for monitoring potential chemical-mediated
26 effects in humans, tests available for measuring responses of the immune system to
27 chemicals that may cause autoimmunity are only poorly validated for clinical purposes.
28
- 29 6. The number of animal models of autoimmunity is extensive. These models represent a
30 variety of systemic and organ-specific diseases, and are mostly used to explore etiology
31 and therapeutic possibilities for certain autoimmune diseases. However, for the purpose
32 of safety evaluation, a general strategy to identify and predict the autoimmunogenic
33 potential of a wide range of chemicals is lacking.
34

1 **Recommendations**

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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.

1 **13. TERMINOLOGY**

2

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

5

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

15

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

20

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

23

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

26

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

31

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

34

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

4
5 **Anemia.** A reduction in number or mass of circulating red blood cells (RBC) that may cause
6 hypoxia in organs or tissue by the reduction in the oxygen-carrying capacity (reduction in
7 haemoglobin concentration) of blood. Anemia is caused either by decreased production or by
8 increased destruction of RBCs. Immune-mediated forms of anemia caused by decreased
9 production of RBCs are autoimmune myelopathies including aplastic anemia, pure red cell
10 aplasia induced by autoantibodies against erythropoietin, \ pernicious anemia caused by
11 autoantibody-mediated vitamin B12 deficiency (autoantibodies against gastric intrinsic factor
12 lead to decreased absorption of vitamin B12). Autoantibodies against structures of RBCs are a
13 main cause of acquired decreased production of RBCs (see also: autoimmune haemolytic
14 anemia).

15
16 **Anergy.** Lack of immune responsiveness (usually defined as lack of response to common recall
17 antigens). The failure of B- or T- cells to proliferate in response to defined autoantigens (\ clonal
18 anergy) is a primary mechanism of \ self-tolerance.

19
20 **Animal models of autoimmunity.** Used for investigations of factors and mechanisms involved
21 in the induction and progression of pathological autoimmunity and disease development with the
22 aim of improvement of diagnosis, prophylaxis and therapy of human autoimmune diseases.
23 However, most experimentally induced or spontaneously occurring animal models usually differ
24 in some aspects from human autoimmunity. Nevertheless, important insights into the
25 pathogenesis of autoimmune diseases can be obtained using animal models, e.g., by
26 immunization, exposure to viruses or \ xenobiotics, thymectomy, manipulation of the \ idiotypic
27 network or genetic engineering (transgenic or knockout animals).

28
29 **Antibody.** An immunoglobulin produced by activated B-cells and plasma cells after exposure to
30 an antigen with specificity for the inducing antigen.

31

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

4
5 **Antigen.** Any compound recognized by antigen-receptor-bearing lymphocytes. Antigens induce
6 immune responses or tolerance. Antigens inducing immune responses only with the help of T-
7 cells are T-dependent antigens, while those that do not need T-help are T-independent antigens.
8 All immunogens are antigens but not all antigens are necessarily immunogens (see also \

9 immunogens).
10
11 **Antigen-presenting cells.** Cells expressing MHC gene products with the capacity to process
12 and present antigen. \ Macrophages, \ dendritic cells, \ B-lymphocytes, and Langerhans' cells
13 are termed professional or constitutive antigen-presenting cells. However, other cells (such as
14 endothelial cells) can acquire the ability to present antigen in certain pathological conditions.

15
16 **Antigen processing and presentation.** Protein antigens are processed (cleaved by enzymes) in
17 various compartments of antigen-presenting cells. The immunogenic peptides interact with the
18 binding sites of MHC class II products (exogenous antigens) or with those in MHC class I
19 products (endogenous antigens, including viruses). The processed antigen-MHC complex is
20 recognized by the antigen receptor complex of T-lymphocytes.

21
22 **Antigenic determinant.** A single antigenic site (epitope) usually exposed on the surface of a
23 complex antigen. Epitopes are recognized by antigen-receptors on T- or B-cells (T-cell epitopes
24 or B-cell epitopes).

25
26 **Antimitochondrial antibodies (AMA).** Autoantibodies producing a mitochondrial staining on
27 cryostat sections of various tissues and on tumor cell monolayers. According to the fluorescence
28 pattern different subtypes can be differentiated. AMA of the subtyp 2 (AMA-M2) are directed
29 against antigens of three related 2-oxo acid dehydrogenase complexes (e.g., the E2 subunit of the
30 pyruvate dehydrogenase complex, PDC-E2) localized to the inner mitochondrial membrane.
31 AMA-M2 is a specific marker of \ primary biliary cirrhosis.

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

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

16
17 **Antinuclear factor (ANF).** Former term for antinuclear antibody.

18
19 **Antiphospholipid antibodies (aPL).** Autoantibodies directed against neutral or negatively
20 charged phospholipids including anti-cardiolipin antibodies (aCl) and Lupus anticoagulant. They
21 are diagnostic markers of the antiphospholipid syndrome (APS), although they are found also
22 in patients with other (autoimmune) diseases and infections.

23
24 **Antiphospholipid syndrome (APS).** One of the most common autoimmune disease
25 characterized by thrombosis, recurrent spontaneous abortions and the presence of
26 antiphospholipid antibodies. APS may occur as an isolated disease (primary APS) or in
27 combination with another autoimmune disease, especially systemic lupus erythematosus
28 (secondary APS).

29
30 **Apoptosis.** Programmed cell death, a physiological process whereby useless and potentially
31 harmful cells are rapidly eliminated without tissue inflammation or damage. Important role in
32 embryogenesis and normal tissue homeostasis, but also involved in the development of
33 malignancy and autoimmunity. The dysfunction of an apoptotic pathway (e.g., defects in certain

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

5
6 **Atherosclerosis.** A type of arteriosclerosis that is characterized by atheroma formation. A
7 multifactorial process leading to accumulation of lipids within the vessel wall, associated with
8 mononuclear cell infiltration and smooth muscle proliferation. Autoimmune mediated
9 inflammation may play an important role in accelerated atherosclerosis in autoimmune rheumatic
10 diseases.

11
12 **Autoantibodies.** Immunoglobulins (antibodies), that are directed against the organisms' own
13 antigens (\ autoantigens). They circulate in the serum but may be also detectable in other body
14 fluids or bound in target tissue structures. Autoantibodies may occur as a part of the natural
15 immunoglobulin repertoire (\ natural autoantibodies) or are induced by different mechanisms
16 (non-natural or pathological autoantibodies). A number of non-natural autoantibodies are
17 diagnostic markers of defined autoimmune diseases regardless of their pathogenetic activity.
18 They may be directed against conserved nonorgan-specific autoantigens (e.g., \ anti-nuclear
19 antibodies), organ-specific extracellular autoantigens (e.g., glomerular basement membrane
20 autoantibodies), organ-specific cellular antigens (e.g., \ islet cell antibodies) or cell specific
21 autoantigens of circulating cells (e.g., \ anti-neutrophil cytoplasmic autoantibodies).

22
23 **Autoantigens.** Self antigens of the organism, which may be targets of autoimmune responses by
24 autoreactive B-cells (see: \ autoantibodies) or T-cells, including proteins (e.g., enzymes,
25 structural proteins), glycoproteins (e.g., beta2 glycoprotein I), nucleic acids (e.g., double-
26 stranded DNA), phospholipids (e.g., cardiolipin) and glycosphingolipids (e.g., gangliosides).

27
28 **Autoimmune diseases.** Disorders that are characterized (i) by the production of autoantibodies
29 or immune effector cells that are autoreactive to self peptides and (ii) by pathological changes
30 (e.g., tissue infiltration, damage and/or dysfunction) that resulted from these immune responses
31 against self antigens (autoantigens).

32

1 **Autoimmune haemolytic anemia (AIHA).** Acquired haemolytic anemia (see also: \ anemia)
2 mediated by autoantibodies against antigens on the organism's own red cell membrane. AIHA
3 may be idiopathic, secondary to lymphoproliferative, autoimmune (e.g., \ systemic lupus
4 erythematosus) or chronic inflammatory disorders, postinfectious or drug-induced (see also: \
5 cold autoantibody type, warm autoantibody type, drug-induced immune haemolytic anemia).
6

7 **Autoimmune hepatitis (AIH).** Chronic autoimmune-mediated hepatic inflammation
8 characterized by antinuclear (ANA), smooth muscle (SMA)/anti-F-actin, liver-kidney
9 microsomal (LKM), and soluble liver antigen (SLA) antibodies. 10-20% of all cases of chronic
10 hepatitis. May be idiopathic (AIH type 1, 2, and 3), part of autoimmune polyendocrine syndrome
11 type 1 (APECED hepatitis) or drug-induced. See also: \ liver-kidney microsomal antibodies
12 (LKM), \ liver specific antigens.
13

14 **Autoimmune lymphoproliferative syndrome (ALPS).** Also known as Canale-Smith
15 syndrome. Characterized by lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias and
16 hypergamma-globulinemia. Associated with defects in Fas-FasL apoptosis signalling pathway
17 due to mutations in the \ Fas gene, the FasL gene, or other genes coding for factors of these
18 pathway.
19

20 **Autoimmune regulator (AIRE).** An important DNA binding protein involved in immune
21 regulation (probably in the establishment and maintenance of tolerance). AIRE is expressed
22 mostly in cells of lymphoid tissues. In the thymus, AIRE is expressed in two types of antigen-
23 presenting cells that are central in the negative selection of self-reactive T-cells. The absence of a
24 functional AIRE protein (caused by mutations in both copies of the AIRE-1 gene) results in the
25 APECED syndrome, also known as autoimmune polyglandular syndrome type 1 (see also: \
26 polyendocrinopathies, autoimmune).
27

28 **Autoimmunity.** Inappropriate reaction of the immune system against the organisms' own
29 antigens (\ autoantigens) that may be either destructive or non-destructive. Destructive
30 autoimmunity is associated with the development of \ autoimmune diseases.
31

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

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

4
5 **B-lymphocytes (B-cells).** Bone-marrow-derived lymphocytes, expressing an antigen-receptor
6 complex composed of membrane-bound immunoglobulin (mIg) and associated molecular chains.
7 B-cell receptors interact with epitopes directly (no MHC restriction). Activated B-lymphocytes
8 produce antibody and are efficient antigen-presenting cells. They are the precursors of plasma
9 cells.

10

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

15 **Cardiolipin.** Main target of antiphospholipid antibodies.

16

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

19

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

22

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

24

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

28

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

32

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

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

4
5 **CD5^{pos} B-lymphocytes.** Lymphocytes of type B1-a, which are predominant in fetal lymphoid
6 organs and in neonatal cord blood. In adults these cells range from 2-6% of total mononuclear
7 cells in peripheral blood. They utilize an immunoglobulin variable gene repertoire different from
8 that of CD5^{neg} B-cells and produce \ natural autoantibodies. The expansion of autoreactive B1-a
9 cells has been reported in peripheral blood of patients with autoimmune diseases (e.g., \
10 rheumatoid arthritis, \
11 Sjögren's syndrome, \
12 antiphospholipid syndrome). In rheumatoid
13 arthritis, these cells can account for up to 60% of circulating B-cells and may produce \
14 rheumatoid factor. The pathological relevance of these observations is unclear, however.

15
16 **CD8.** A cell surface molecule belonging to the immunoglobulin superfamily of molecules.
17 Marker of suppressor and cytotoxic T-cells. As an adhesion molecule, it interacts with the MHC
18 class I gene product.

19
20 **CD8^{pos} T-suppressor cells.** Regulatory T-cells that inhibit the proliferation of antigen-specific
21 T-cells. Three different subpopulations have been functionally identified in humans. Functional
22 alterations were shown to be associated with the relapse of autoimmune diseases.

23
24 **CD16.** Low-affinity Fc γ receptor (Fc γ RIII) expressed mainly on NK-cells, granulocytes and
25 macrophages, mediating ADCC.

26
27 **CD23.** Low-affinity Fc ϵ receptor induced by IL-4 and expressed on activated B-cells and
28 macrophages.

29
30 **CD25.** Alpha-chain of the interleukin 2 receptor expressed mainly on CD4^{pos} T-cells.

31
32 **CD40 ligand (CD40L):** Essential molecule for normal switching signalling through binding to
33 CD40 on B-cells. The interaction of CD40L and CD40 is also critical for optimal T cell function.
See also: \
hyper IgM syndrome.

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

4
5 **Cell-mediated or cellular response.** A specific immune response in which T-lymphocytes
6 mediate the effects, either through the release of cytokines or through cytotoxicity.

7
8 **Chemokines.** Large family of small secreted proteins (8-15 kDa) that control the trafficking of
9 leukocyte subpopulations, induce leukocyte activation and control lymphocyte differentiation
10 and effector function. May play an important role in the pathogenesis of autoimmune diseases,
11 because the migration and accumulation of leukocytes in the target organs are a critical step for
12 this.

13
14 **Class I MHC gene products.** Antigens encoded by the MHC class I genes are expressed on all
15 nucleated cells. They present antigen-derived peptides of endogenous origin.

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

18
19 **Clonal anergy.** State of specific functional unresponsiveness. Failure of B- or T-cells to
20 proliferate in response to antigen by downregulation of the antigen receptor complex and/or
21 cytokine receptors and costimulatory molecules. Primary mechanism involved in the induction
22 and maintenance of \ self-tolerance.

23
24 **Clonal deletion.** Elimination (e.g., by \ apoptosis, receptor editing) of self-reacting B- or T-cells
25 during their maturation in central or peripheral lymphoid tissues. Primary mechanism involved in
26 the induction and maintenance of \ self-tolerance.

27
28 **Clonal indifference (ignorance).** Failure of B- or T-cells expressing anti-self receptors to
29 interact with antigen (e.g., by low valency, low concentration or sequestration of antigens; low
30 receptor avidity; lack of costimulatory molecules). Primary mechanism involved in the induction
31 and maintenance of \ self-tolerance.

32

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

5
6 **Complement system.** A group of serum proteins with the capacity to interact with each other
7 when activated. The chain reaction of the activated complement components results in formation
8 of a lytic complex and several biologically active peptides of low relative molecular mass
9 (anaphylatoxins). The system can be activated by antigen-antibody complexes (classical
10 pathway) and by other components, e.g., bacteria (alternative pathway). As an effector mecha-
11 nism of the humoral immune response, the activated complement system facilitates opsonization,
12 phagocytosis and lysis of cellular antigens. Some defects in components of complement are
13 associated with autoimmune diseases (see \ complement deficiency).

14
15 **Complement deficiency.** Congenital deficiencies in the various components of the complement
16 system. Rheumatic disorders (mainly \ systemic lupus erythematosus) are associated with
17 deficiencies of the early components of the classical pathway. More than 30% of individuals with
18 C2 deficiency and nearly 80% with either C3 or C4 deficiency have an autoimmune
19 manifestation.

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

24
25 **Cross-reactivity.** The ability of an antibody or a T-cell, specific for one antigen, to react with a
26 second antigen; a measure of relatedness between two antigenic substances, and/or
27 polyspecificity of the antibody molecule (e.g., some rheumatoid factors), or of the T-cell
28 receptor.

29
30 **Cryoglobulinemic vasculitis.** Cutaneous or systemic vasculitis caused by frigolabile proteins (\
31 cryoglobulins, cryofibrinogen) that leads to increased viscosity, protein precipitation or
32 gelatinification, complement activation and endothelial cell damage, especially in the cold.

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

3

4 **Cryoglobulins.** Precipitating immunoglobulins, forming insoluble aggregates at temperatures
5 below 25⁰C. Many cryoglobulins function as autoantibodies (e.g., rheumatoid factor).

6 Cryoglobulins are found in lymphoproliferative diseases, a number of autoimmune diseases as
7 well as chronic infections. They can lead to vasculitic and secondary thrombotic manifestations
8 (∖ cryoglobulinemic vasculitis, glomerulonephritis).

9

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

15

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

19

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

24

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

27

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

30

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

32

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

6
7 **Double-stranded DNA (dsDNA).** Main target of autoantibodies in patients with \ systemic
8 lupus erythematosus. **DsDNA autoantibody** is a diagnostic marker and classification criterium
9 of this disease.

10
11 **D-penicillamine.** A drug that is able to induce a variety of autoantibodies and autoimmune
12 diseases (e.g., \ myasthenia gravis, polymyositis). Disease usually remits within 1 year after the
13 medication is stopped.

14
15 **Drug-induced lupus (DIL).** A lupus-like disorder induced by various medications that is
16 mainly characterized by the occurrence of arthralgia, myalgia, pleuritis, erythema, fever and anti-
17 nuclear antibody (ANA) production. The clinical symptoms disappear within a few days to
18 weeks after withdrawal of the causative drug, and the associated autoimmune phenomena
19 disappear within the course of a year. **Classical DIL-inducing drugs** are procainamide,
20 hydralazine and quinidine.

21
22 **Drug-induced immune haemolytic anemia.** Anemia caused by drug-mediated immune
23 haemolysis of red blood cells (RBC) through different antibody-mediated mechanisms: (i) drug
24 adsorption mechanism (antibody directed against the drug bound to RBC surface antigen), (ii)
25 ternary (immune) complex mechanism (antibody form a trimolecular complex with the drug and
26 RBC membrane antigen) and (iii) true autoantibody-mediated mechanism (drug-induced
27 antibodies bind RBCs in the absence of the drug).

28
29 **Eczema.** A dermatitis characterized by non-contagious inflammation of skin with typical
30 clinical (itch, erythema, papules, seropapules, vesicles, squames, crusts, lichenification) and
31 dermatohistological (spongiosis, acanthosis, parakeratosis, lymphocytic infiltration) findings.
32 Often due to sensitization.

33

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

3
4 **Enzyme-linked immunosorbent assay (ELISA).** An assay in which an enzyme is linked to an
5 antibody and a labelled substance is used to measure the activity of bound enzyme and, hence,
6 the amount of bound antibody. With a fixed amount of immobilized antigen, the amount of
7 labelled antibody bound decreases as the concentration of unlabelled antigen is increased,
8 allowing quantification of unlabelled antigen (**competitive ELISA**). With a fixed amount of one
9 immobilized antibody, the binding of a second, labelled antibody increases as the concentration
10 of antigen increases, allowing quantification of antigen (**sandwich ELISA**). ELISAs are used for
11 the specific determination of \ autoantibodies.

12
13 **Epidemiology.** The study of the distribution and determinants of health-related states or events
14 in specified populations, and the application of this knowledge to manage health problems.

15
16 **Epitope.** Antigenic determinant, a structure of biological molecules that mediate specific
17 recognition by the immune system.

18
19 **Epitope spreading.** Increase in the number of epitopes targeted by autoantibodies and/or T-cells.
20 May be on the same autoantigen (intramolecular epitope spreading) and/or on other autoantigens
21 (intermolecular epitope spreading). Characteristic sign of progression of autoimmune disease
22 from initial activation to a chronic state.

23
24 **Exogen-autoimmune encephalomyelitis (EAE).** Autoimmune demyelinating disease induced
25 in genetically susceptible mice, rats or marmosets by immunization with myelin proteins or
26 peptides. Animal model for \ multiple sclerosis.

27
28 **Exogen-allergic encephalomyelitis:** former term for \ exogen-autoimmune encephalomyelitis
29 (EAE).

30
31 **Experimental autoimmune thyroiditis (EAT).** Autoimmune thyroiditis experimentally induced
32 in several strains of mice and rats by immunization with thyroglobulin or by neonatal
33 thymectomy.

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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.

- 1 **Glomerular basement membrane (GBM).** Target of autoantibodies in patients with \
- 2 Goodpasture's disease. The autoantigenic epitope is a peptide on the $\alpha 3$ chain of type IV
- 3 collagen which is also found in renal tubular and alveolar basement membrane.
- 4 **Glomerulonephropathy.** Disease of the glomeruli, which may show either thickening of the
- 5 basement membrane membranous glomerulopathy associated with IgG deposits □ due to the
- 6 accretion of proteins, or a minimal change glomerulopathy, in which there is functional damage
- 7 but little structural change by light microscopy.
- 8
- 9 **Glutamic acid decarboxylase (GAD).** Main autoantigen in \ diabetes mellitus type 1 and Stiff-
- 10 Person-Syndrome (a neurologic autoimmune disease). Localized in pancreatic beta-cells and
- 11 GABAergic neurons.
- 12
- 13 **Goodpasture's disease/syndrome.** An autoimmune pulmonary-renal syndrome characterized by
- 14 pulmonary hemorrhage, glomerulonephritis, and production of autoantibody to \ glomerular
- 15 basement membrane (GBM); Anti-GBM disease.
- 16
- 17 **Graves' disease.** Hyperthyroidism associated with diffuse hyperplastic goiter resulting from
- 18 production of a thyroid-stimulating hormone receptor (TSH-R) binding autoantibody.
- 19
- 20 **Hapten.** A non-immunogenic compound of low relative molecular mass which becomes
- 21 immunogenic after conjugation with a carrier protein or cell and in this form induces immune
- 22 responses. Antibodies, but not T-cells, can bind the hapten alone in the absence of carrier.
- 23
- 24 **Hashimoto's thyroiditis.** Goitrous form of diffuse autoimmune thyroiditis. See also: \
- 25 thyroiditis, autoimmune.
- 26
- 27 **Helper T-lymphocyte.** A functional subpopulation of T-cells (expressing CD4 antigen) that
- 28 help to generate cytotoxic T-cells and cooperate with B-cells in the production of an antibody
- 29 response. Helper T-cells recognize antigen in association with MHC class II gene products.
- 30 Depending on their capacity to produce various cytokines one can functionally differentiate \
- 31 Th1 (IL-2 and IFN gamma producing) and \ Th2 (IL-3, IL-4 and IL-6 producing) cells.
- 32

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

5
6 **Hepatitis, chronic.** see: \ autoimmune hepatitis.

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

11
12 **Humoral immune response.** An immune response in which specific antibodies induce the
13 effector functions (such as phagocytosis and activation of the complement system).

14
15 **Hypergammaglobulinemia.** Increase of gammaglobulins in the blood by paraproteinemia or
16 increased production of \ immunoglobulins.

17
18 **Hyper IgM syndrome (HIGM):** Primary T cell defect due to mutations in the CD40 ligand.
19 Characterized by recurrent (opportunistic) infections and very low levels of IgG and IgA.
20 Autoimmune manifestations (e.g., cytopenia, arthritis, sclerosing cholangitis) are often seen.

21
22 **Hyperreactivity.** An abnormally increased response to a stimulus.

23
24 **Hypersensitivity.** Abnormally increased immunologically mediated response to a stimulus.
25 Sometimes used loosely for any increased response.

26
27 **Hypersusceptibility.** Adverse effects in an individual occurring under exposure conditions that
28 result in no effects in the great majority of the population or an individual exhibiting exaggerated
29 effects in comparison with the great majority of those showing some adverse effects.

30
31 **Hyperthyroidism.** Hyperactivity of the thyroid gland. Autoimmunity is the commonest cause of
32 hyperthyroidism, accounting for 60-80% of cases. See also: \ Graves' disease.

33

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

4
5 **Idiopathic thrombocytopenic purpura (ITP).** Autoantibody-mediated thrombocytopenia
6 (autoimmune thrombocytopenic purpura).

7
8 **Idiopathic.** A term that describes a "primary" symptom or disease, in which no underlying
9 cause or associated disorder could be found. In most cases autoimmune processes are involved in
10 the pathogenesis (e.g., idiopathic thrombocytopenic purpura, idiopathic Addison's disease).

11
12 **Idiosyncrasy.** An unusual individual reaction to food or a drug not related to allergy or \
13 autoimmunity.

14
15 **Idiotypic.** Unique, genetically controlled determinants present on \ immunoglobulin variable
16 domains and determine the antibody specificity.

17
18 **Idiotypic network.** Feedback inhibition of ongoing B- or T-cell responses by a network of (anti-
19 idiotypic--idiotypic) interactions. Secondary mechanism involved in the induction and
20 maintenance of \ self-tolerance.

21
22 **Immune complexes (IC).** Antigen-antibody complexes formed every time antibody meets
23 antigen. May become pathogenic by triggering a variety of inflammatory processes if not
24 removed effectively from circulation or if formed in situ. IC play a role in vasculitic
25 manifestations of autoimmune diseases (e.g., lupus nephritis).

26
27 **Immune deviation.** A regulatory mechanism of the preferential activation of one arm (cellular
28 vs. humoral; see also \ Th1- and \ Th2-cells) of the adaptive immune system at the expense of
29 the other. Although not a form of true tolerance this regulatory mechanism may be involved in
30 the induction and maintenance of \ self-tolerance.

31
32 **Immunodeficiency.** Defects in one or more components of the immune system resulting in
33 inability to eliminate or neutralize non-self antigens. Congenital or primary immunodeficiencies

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

11

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

16

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

25

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

31

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

34

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

6

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

9

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

17

18 **Interclonal competition.** Favouring of foreign-specific lymphocytes at the expense of self-
19 specific lymphocytes. Secondary mechanism involved in the induction and maintenance of \
20 self-tolerance.

21

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

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

- 1
- 2 **IPEX.** X-linked syndrome characterized by immunodysregulation, polyendocrinopathy (type 1
3 diabetes, thyroiditis), hemolytic anemia, thrombocytopenia, dermatitis and enteropathy, caused
4 by mutations in FOXP3.
- 5
- 6 **Iron.** Vital metal for the proliferation of all cells including those of the immune system. May be
7 involved in the induction of autoimmunity by influencing the antigen presentation (catalysing the
8 production of cryptic epitopes of autoantigens).
- 9
- 10 **Islet cell antibodies (ICA).** Autoantibodies reacting with endocrine (pancreatic islet) cells and
11 detectable by indirect immunofluorescence on pancreas cryostat sections. Diagnostic marker of
12 diabetes mellitus type 1.
- 13
- 14 **Kidney diseases, autoimmune.** May be due to immunologic reaction to renal antigens (glomerular
15 basal membrane, Goodpasture's syndrome) or part of systemic autoimmune disease
16 (e.g., systemic lupus erythematosus, ANCA-associated vasculitides).
- 17
- 18 **Langerhans' cells.** Bone-marrow-derived epidermal cells with a dendritic morphology,
19 expressing CD1 marker in humans and containing the cytoplasmic organelle, called the Birbeck
20 granule. They express Class II MHC antigen and are capable of antigen presentation (see also
21 dendritic cells).
- 22
- 23 **Lambert-Eaton myasthenic syndrome (LEMS).** Paraneoplastic neurological disorder
24 associated with small cell lung cancer and caused by autoantibodies against voltage-gated
25 calcium channels.
- 26
- 27 **Leukocytopenia.** Amount of leukocytes below normal values. Characteristic feature of systemic
28 autoimmune diseases (e.g., Felty's syndrome, systemic lupus erythematosus, Sjögren's
29 syndrome, mixed connective tissue disease).
- 30
- 31 **Leukocytosis.** Abnormal increase in the number of white blood cells.
- 32

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

3

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

10

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

18

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

21

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

25

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

32

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

7
8 **Major histocompatibility complex (MHC).** A cluster of genes encoding cell surface antigens
9 that are polymorphic within a species and have a crucial function in signalling between
10 lymphocytes and cells expressing antigen and in recognition of self.

11
12 **Microchimerism.** A state, in which a small number of cells or DNA from one individual
13 harbored in another individual. Fetal as well as maternal microchimerism may be involved in the
14 pathogenesis of autoimmune disease (e.g., systemic sclerosis).

15
16 **Microscopic polyangiitis (MPA).** ANCA-associated necrotizing, pauci immune vasculitis of
17 the small vessels (capillaries, venules, arterioles) frequently associated with rapidly progressive
18 glomerulonephritis and/or hemorrhagic alveolitis as well as autoantibodies against \
19 myoleoperoxidase.

20
21 **Mitogen.** A substance that causes cells to synthesize DNA and proliferate without acting as an
22 antigen.

23
24 **Mixed connective tissue disease (MCTD).** Systemic autoimmune disease with features of \
25 systemic lupus erythematosus, \
26 systemic sclerosis, and dermatomyositis/polymyositis and high
27 titered autoantibodies against U1-RNP specific proteins.

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

30
31 **Monocyte.** Bone-marrow-derived mononuclear phagocytic leukocyte, with bean-shaped nucleus
32 and fine granular cytoplasm containing lysosomes, phagocytic vacuoles and cytoskeletal
33 filaments. Once transported to tissues they develop into macrophages.

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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 exposed 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 isotype 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-

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

4
5 **Natural killer (NK) cell.** A subset of lymphocytes found in blood and some lymphoid tissues,
6 derived from the bone marrow and appearing as large granular lymphocytes (LGL). NK-cells
7 possess the capacity to kill certain tumour cells or virus-infected normal cells. The killing is not
8 induced by specific antigen and is not restricted by MHC molecules.

9
10 **Nephritis, autoimmune.** Inflammation of the kidney (proteinuria and nephritic urinary
11 sediment) due to immunologic reaction to renal antigens (anti-GBM disease, \ Goodpasture's
12 disease; autoimmune tubulointerstitial nephritis with antibody to tubular basement membrane) or
13 as part of systemic autoimmune diseases independent of renal autoantigens (lupus nephritis in \
14 systemic lupus erythematosus, interstitial nephritis in \ Sjögren's syndrome, nephritis in \
15 ANCA-associated vasculitis, cryoglobulinemic vasculitis or hypocomplementemic urticarial
16 vasculitis syndrome).

17
18 **Nephropathy.** Disease of the kidney that may involve either or both the glomeruli (specialized
19 structures where blood is filtered) and the renal tubules (connected structures where the
20 composition of the filtrate is greatly modified in accordance with the physiological needs of the
21 body).

22
23 **Nephrotic syndrome.** A clinical disease in which damage to glomeruli has caused leaky
24 filtration, resulting in major loss of protein from the body

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

33

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

5
6 **Natural resistance-associated macrophage protein (NRAMP1).** Iron transporter that plays a
7 critical role in macrophage activation and differentiation. Allele 3 of the NRAMP1 promoter is
8 associated with autoimmune disorders (e.g., rheumatoid arthritis, juvenile rheumatoid arthritis,
9 type 1 diabetes mellitus, multiple sclerosis).

10

11 **Oncogenes.** Genes which can potentially induce neoplastic transformation. See also \ Proto-
12 Oncogenes.

13

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

17

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

19

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

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

28

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

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

3
4 **Peripheral neuropathies, autoimmune.** Acute or chronic inflammatory neuropathies leading to
5 demyelination and axonal damage of nerves and nerve roots associated with high-titred
6 autoantibodies against \ gangliosides (e.g., Guillain-Barré syndrome, Miller-Fisher syndrome,
7 acute sensory ataxic neuropathy).

8
9 **Pernicious anemia.** End stage of 10-15% of \ autoimmune gastritis due to vitamin B12
10 malabsorption caused by depletion of gastric parietal cells and autoantibodies against intrinsic
11 factor. Associated with a variety of autoimmune endocrine diseases (e.g., \ Hashimoto's
12 thyroiditis, \ Addison's disease) and autoimmune myasthenic syndromes.

13
14 **Photosensitivity.** Skin reddening due to an abnormal reaction to sunlight. A characteristic
15 symptom of systemic autoimmune diseases (e.g., \ systemic lupus erythematosus, \ mixed
16 connective tissue disease), cutaneous and \ subacute cutaneous lupus erythematosus.

17
18 **Plasma cell.** A terminally differentiated B-lymphocyte with little or no capacity for mitotic
19 division, that can synthesize and secrete antibody. Plasma cells have eccentric nuclei, abundant
20 cytoplasm and distinct perinuclear haloes. The cytoplasm contains dense rough endoplasmic
21 reticulum and a large Golgi complex.

22
23 **Polyendocrinopathies, autoimmune.** Autoimmune diseases affecting multiple endocrine
24 organs: (i) The autoimmune polyglandular syndrome type 1 (**APS-1**) is characterized by
25 mucocutaneous candidiasis in association with endocrine manifestation (also called **APECED**
26 **syndrome**: autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy), while (ii) the
27 autoimmune polyglandular syndrome type 2 (**APS-2**) exhibits any combination of adrenal
28 insufficiency (see: \ Addison's disease), type 1 diabetes mellitus (see: \ diabetes mellitus,
29 insulin-dependent), lymphocytic thyroiditis (see: \ thyroiditis, autoimmune),
30 hypoparathyroidism, and gonadal failure. In both types organ-specific autoantibodies against a
31 variety of endocrine glands are detectable. See also: \ autoimmune regulator (AIRE).

32

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

3
4 **Primary biliary cirrhosis (PBC).** Autoimmune liver disease that results in the destruction of
5 bile ducts leading to fibrosis and cirrhosis. PBC-specific are \ antimitochondrial antibodies
6 (AMA) directed against proteins of the pyruvate dehydrogenase complex (mainly the E2
7 subunit).

8
9 **Primary sclerosing cholangitis (PSC).** Chronic, nonbacterial inflammatory narrowing of the
10 bile ducts. Often associated with ulcerative colitis.

11
12 **Primary myxedema.** Atrophic form of diffuse autoimmune thyroiditis (see also thyroiditis,
13 autoimmune).

14
15 **Prolactin.** A versatile hormone that is involved in the regulation of proliferation and
16 differentiation of a variety of cells in the immune system. May play a role in the pathogenesis
17 and clinical expression of autoimmune diseases (e.g., \ systemic lupus erythematosus).

18
19 **Proteinase 3 (PR3).** This multifunctional enzyme of azurophilic granules of neutrophils and
20 monocytes is the major target of cANCA (see: \ anti-neutrophil cytoplasmic autoantibodies).

21 **PR3 autoantibodies** are diagnostic markers for \ Wegener's granulomatosis (WG) and involved
22 in the pathogenesis of this disease. They are also found at low frequencies in patients with other
23 autoimmune systemic vasculitic diseases.

24
25 **Proteinuria.** Main symptom of \ nephritis.

26
27 **Proto-Oncogenes.** Genes that may be involved in neoplastic transformation. The products of
28 proto-oncogenes are important regulators of biological processes (e.g. growth factors, growth
29 factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, transcription
30 factors). Mutations or aberrant expression of some proto-oncogenes may be involved in the
31 pathogenesis of autoimmune diseases. See also \ bcl-2.

32
33 **Rate (epidemiology).** The frequency with which an event occurs in a defined population.

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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/δ receptors).

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.

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

5
6 **Sjögren's syndrome.** Chronic inflammatory autoimmune disease of the exocrine glands of
7 unknown etiology. Its primary symptoms are keratoconjunctivitis sicca and xerostomia. Two
8 types of Sjögren's syndrome are distinguished: a primary (isolated) type and a secondary type
9 associated with another underlying autoimmune disease (e.g., \ rheumatoid arthritis, \ systemic
10 lupus erythematosus, \ systemic sclerosis, primary biliary cirrhosis, autoimmune hepatitis,
11 multiple sclerosis, autoimmune thyroiditis, etc.). Ro/SS-A and La/SS-B autoantibodies are used
12 as classification criteria.

13
14 **Spontaneous autoimmune thyroiditis (SAT).** Autoimmune thyroiditis that develops
15 spontaneously (without any apparent cause or manipulation) in certain strains of mice and rats
16 (e.g., NOD mice, BB and BUF rats) as well as in other animals (e.g., OS chickens, marmoset
17 monkeys, beagles).

18
19 **Stem cell.** Pluripotent cells, representing 0.01% of bone marrow cells, having the capacity for
20 self renewal, and committed to differentiate along particular lineages, e.g., erythroid,
21 megakaryocytic, granulocytic, monocytic and lymphocytic. Cytokines stimulate the proliferation
22 and maturation of distinct precursors.

23
24 **Subacute cutaneous lupus erythematosus (SCLE).** A chronic remitting form of dermatitis
25 characterized by severe photosensitivity and Ro/SS-A and La/SS-B autoantibodies.

26
27 **Suppression.** Dominant immunological tolerance, a phenomenon which plays an active role in
28 regulating T- and B-cell responses to both foreign and self antigens (\ suppressor T-lymphocyte).
29 The downregulation of responses to self antigens is a major regulatory mechanism involved in
30 the induction and maintenance of \ self-tolerance.

31

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

4

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

11

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

18

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

23

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

27

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

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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.

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

4
5 **Tissue transglutaminase (tTG).** Main target of autoantibodies in celiac disease.

6
7 **T-lymphocytes (T-cells).** Thymus-dependent lymphocytes which differentiate in the thymus to
8 express T-cell receptor molecules (TCRs) that are specific for complexes comprising short
9 peptides bound to and presented by major histocompatibility complex (MHC) molecules.
10 Different subpopulations of regulatory and effector cells, see cytotoxic, helper, regulatory
11 and suppressor T-cells.

12
13 **Tolerance.** Persistent condition of specific immunological unresponsiveness, resulting from
14 previous non-sensitizing exposure to the antigen. See also: self-tolerance.

15
16 **Urticaria.** Transient eruption of skin characterized by erythematous or oedematous swelling
17 (wheal) of the dermis or subcutaneous tissue.

18
19 **Vasculitis.** Acute or chronic inflammation of the vessel walls that can lead to necrosis, fibrosis or
20 thrombosis. Autoimmunity plays an important role in some vasculitides (e.g., ANCA-
21 associated vasculitides, Goodpasture's disease, cryoglobulinemic vasculitis).

22
23 **Vetoing.** Elimination (apoptosis) of the self-peptide-MHC complex recognizing lymphocyte
24 by the self-peptide presenting (veto) cell. A less important regulatory mechanism of self-
25 tolerance.

26
27 **Warm autoantibody type.** Autoantibodies that react optimally at higher temperatures (37°C)
28 with surface antigens of red blood cells. They mediate autoimmune haemolytic anemia.

29
30
31 **Wegener's granulomatosis (WG).** Granulomatous inflammation involving the respiratory
32 tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries,
33 venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.

1

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

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