



**Review**

## Koch's Postulates and Autoimmunity: an Opposing Viewpoint

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**Abstract.** Autoimmunity is characterized as a state of abnormal specific humoral and cell-mediated responses against constituents of body tissues. One time-honored approach to explaining the pathogenesis of autoimmunity has been application of the Koch's postulates, on loan from the field of microbiology suggesting that autoantibodies and/or autoreactive T cells are the presumed "pathogens" of autoimmunity, and that passive transfer of these autoimmune factors to susceptible animals will result in the induction of the autoimmune disease. We suggest that autoimmunity is **not** in many cases due to the presence of factors leading to the autoimmune response in those susceptible. Instead, it is the **lack** of a factor which leads to the development of autoimmunity, a factor (cytokine, protein, gene, etc.) which is present in the healthy individual and normally protects in from disordered immune regulation. We propose to direct more research into therapeutic modulation of autoimmunity by administration of putative "protective factors", rather than by attempts to depress or remove autoreactive cells and antibodies from the autoimmune.

**Key words:** autoimmunity; autoantibodies; autoreactive cells; pathogenesis.

Autoimmunity is characterized as a state of abnormal specific humoral and cell-mediated responses against constituents of body tissues. Recent breakthroughs in immunology research have directed increasing attention to the pathogenetic mechanisms leading to the loss of tolerance to self-antigens, and autoimmune disease. Traditional research in this field has focused on the animal model or the human with autoimmune manifestations, attempting to define the abnormal factor or element leading to and responsible for the autoimmune process.

One time-honored approach to explaining the pathogenesis of autoimmunity has been application of the Koch's postulates, on loan from the field of microbiol-

ogy<sup>5</sup>. These stipulations must be demonstrated in order to prove a causal relationship between a microorganism and the disease in question. Put simply, it must be shown that:

- 1) the microorganism is regularly isolated from the cases of the illness;
- 2) the organism must be grown in pure culture;
- 3) when such a pure culture is inoculated into a susceptible animal species, the typical disease must result;
- 4) from each experimentally induced disease, the microorganism must again be isolated.

Inserting autoantibodies and/or autoreactive T cells as the presumed "organism" (pathogenetic factor), and autoimmunity as the "disease" into these Koch's

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postulates, will indeed seem to support a relationship of causality between autoantibodies and autoreactive T cells, to the autoimmune disease process.

Despite the appeal of this theory, when so presented, certain lines of evidence have raised some basic doubts regarding its validity. As a rule, adoptive transfer of disease from a sick animal or human to a healthy host with autoantibodies or autoreactive T cells is usually unsuccessful, without co-application of special procedures such as irradiation and/or cytotoxic therapy, as we will show below. In addition, autoimmunity is inducible in the normal host by immunosuppressive therapy.

Koch's postulates would predict that therapy intended to decrease production (steroids, cytotoxic drugs) or enhance clearance (plasmapheresis) of autoantibodies or autoreactive T cells would be highly successful in autoimmune disease. We find it highly significant that such therapy as directed by Koch's postulates has only resulted in suppression of disease manifestations, and at best only led to a temporary remission in the course of the disease. Frequently, such therapeutic modalities subject the patient to significant morbidity and even mortality. Perhaps new concepts of pathogenesis are needed, with more specific and effective treatments to follow.

We suggest that autoimmunity is **not** in many cases due to the presence of factors leading to the autoimmune response in those susceptible. Instead, it is the **lack** of a factor which leads to the development of autoimmunity; a factor (cytokine, protein, gene, etc.) which is present in the healthy individual and protects it from disordered immune regulation. We will re-examine the Koch's postulates as they relate to autoimmunity, and show that recent developments cast some doubt on traditional theories, and indeed hint towards the presence of such a "protective factor" in the non-autoimmune host. Finally, we propose to direct more research into therapeutic modulation of autoimmunity by administration of putative "protective factors", rather than by attempts to depress or remove antigens and antibodies from the autoimmune.

### Adoptive Transfer of Autoimmunity

*Are B cells producing autoantibodies the "pathogenic organism" in autoimmune disease?*

*Transferability and inducibility of autoimmune from the mother to the newborn.* A natural, easily repeated "experiment" in which transferability of autoimmunity can be examined is the pregnant, autoimmune individ-

ual. Despite the presence of supposedly pathogenic autoantibodies in high titer, only rarely are immune manifestations apparent in the fetus.

**D e r m a t o m y o s i t i s / p o l y m y o s i t i s.** No neonatal effects of dermatomyositis/polymyositis have been described in surviving children from mothers with the diseases<sup>30</sup>. In one autopsy of a neonatal death, the newborn had no abnormal pathologic findings in the skin or muscle<sup>47</sup>.

**S c l e r o d e r m a.** Although rates of prematurity, intrauterine growth retardation, intrauterine and neonatal death are higher than for a normal pregnancy, no reports exist describing transfer of the disease to the newborn (only 3 cases of limited areas of sclerosis)<sup>3</sup>.

**R h e u m a t o i d a r t h r i t i s.** A successful pregnancy, normal delivery, and a healthy infant is the usual and expected course in pregnant patients with rheumatoid arthritis. Moreover, pregnancy has a known beneficial effect on the course of the disease<sup>4</sup>.

**I m m u n e t h r o m b o c y t o p e n i c p u r p u r a.** There is no good correlation between either maternal platelet counts or maternal platelet-associated antibody levels and fetal platelet counts at the time of delivery. If thrombocytopenia is present in the infant, it is usually not severe, and recovery can be expected in 4–6 weeks<sup>41</sup>.

Perhaps the most classic example given to demonstrate the transferability of autoimmunity from the mother to the newborn by autoantibodies is the neonatal lupus syndrome, highly associated with the anti-Ro antibody. However, several datum detract from a simple causal relationship.

- Neonatal lupus is a very rare disease, relative to the incidence of systemic lupus erythematosus (SLE) in females of child bearing age. Almost all the reports in the literature are single case reports. PETRI et al.<sup>38</sup> in 1989 were able to gather only 229 cases altogether, and thought it was likely that some of the cases were multiply reported.

- Assuming that transplacentally transferred anti-Ro from the mother is the cause of cutaneous rash of neonatal lupus, lesions should disappear by 6 months. However, several reports of lesions appearing beyond 1 year have been published<sup>29</sup>.

- Autopsy studies of neonatal lupus with congenital heart block have been done, and found besides IgG, also IgM and IgA which cannot be transferred transplacentally<sup>45</sup>. This finding suggested that the staining was non specific, and due only to tissue damage. Demonstration of the antibody in cardiac tissue, while suggestive, cannot and should not be construed as conclusive evidence for pathogenesis.

– Anti-Ro is not sufficient to cause lupus, as demonstrated by WATSON et al.<sup>52</sup> who found only one case of neonatal lupus in a retrospective study of 67 live births to mothers with anti-Ro.

Although there are other instances in which there is a more clear relationship between transferable autoantibodies originating in the mother and disease in the newborn (neonatal myasthenia gravis, thyroid disease), these are the exceptions rather than the rule. Autoimmune disease in the newborn tends to be only transient, and maternal autoantibodies do not initiate a self-perpetuating autoimmune process.

*Transgenic mice.* Koch's fourth postulate states that from each case of experimentally induced disease, the microorganism must be again isolated. A corollary would be that genes encoding pathogenic autoantibodies would cause autoimmune disease in transgenic mice. OKAMOTO et al.<sup>34</sup> published their model of double transgenic mice bearing immunoglobulin-chain genes for an antibody against mouse erythrocytes. No consistent clinical expression was found, despite the fact that most B cells expressed on their surface the autoantibody against the erythrocyte. Only 5% of the mice developed significant anemia, while 51% were tolerant with no evidence of disease. ERIKSON et al.<sup>14</sup> created a model of transgenic mice in a non-lupus strain, using the heavy chain variable gene of a monoclonal anti-DNA antibody which rises spontaneously in the autoimmune MRL-lpr/lpr mouse. Despite the high frequency of anti-DNA carrying B cells in the transgenic mice, serum titers of anti-DNA were not higher than those found in normal mice. These results showed that anti-DNA antibodies were regulated in the normal, non-autoimmune animals. Despite the fact that most of the B cells in the transgenics were specific for ssDNA, they nevertheless did not differentiate into immunoglobulin-secreting cells. This suggested to ERIKSON et al.<sup>14</sup> and as we are hypothesizing, that the normal host can regulate disease-associated autoantibodies, and that autoimmune disease results from breakdown, or lack of regulation. It has been further shown that in normal mice B cells expressing anti-DNA specificity are deleted in the bone marrow at the pre-B to immature B transitional stage<sup>6</sup>.

It has been suggested that autoreactive anti-DNA B cells can escape negative regulation even in the normal host by a process called receptor editing<sup>7</sup>, but even in those circumstances features of autoimmunity were very mild and the mice did not express the full clinical picture of lupus<sup>40</sup>. Similarly, TSAO et al.<sup>48</sup> generated transgenic mice in a non-lupus strain that expressed both heavy and light chain genes derived from a hybri-

doma secreting a pathogenic IgG2a monoclonal antibody specific for both single and double stranded anti-DNA. Although multiple lines of transgenic mice had high levels of circulating, transgene-encoded anti-DNA, in no case were these levels comparable to those present in the mouse strain with spontaneous lupus (aged BW). Proteinuria and azotemia in the transgenic, while present, was less severe, and did not progress over time. Specifically, no transgenic mice died of fatal nephritis (the most common reason for mortality in the BW mouse). TSAO et al.<sup>48</sup> suggest that the normal mice, despite the production of anti-DNA in this model, lack factors present in the BW predisposing towards the disease. Alternatively, we propose that it is the BW strain that lacks a factor protecting it from the development of disease, while the normal mice are relatively safe from autoimmunity despite a genetic repertoire of autoantibodies, because of this protective factor.

*Severe combined immunodeficient (SCID) mice.* SCID mice have an autosomal recessive defect preventing development of functional lymphocytes. It was shown that human fetal lymphoid tissue or peripheral adult blood lymphocytes can survive in SCID mice, thereby allowing study of human autoimmune diseases. KRAMS et al.<sup>23</sup> injected peripheral blood lymphocytes from normal volunteers and patients with primary biliary cirrhosis (PBC), into SCID mice. Although the biliary lesions in the SCID mice who received lymphocytes from the PBC patients were more severe, those mice with a graft from normal donors also developed a biliary inflammatory reaction. Therefore, what was observed may not have been early lesions of PBC, but rather a graft-versus-host reaction. TIGHE et al.<sup>46</sup> performed adoptive transfer of rheumatoid arthritis synovial cells with peripheral blood lymphocytes into SCID mice. Mononuclear cells from synovial fluid or tissue resulted in a much higher IgM-rheumatoid factor production in the mice than that of peripheral lymphocytes from patients or normal donors. However, autoantibody production gradually decreased with time even when total immunoglobulin levels increased, and elevated production could not be induced by antigenic stimulation. In addition, even at their peak level overall levels of rheumatoid factors were not high, and inflammatory joint injury was absent. DUCHOSAL et al.<sup>11</sup> transferred peripheral blood leukocytes from 5 SLE patients into 15 SCID mice. Reconstituted mice showed production of human IgG, reaching maximum levels 2 months after transfer and gradually declining over the next 4–7 months, and with autoantibodies characteristic of their donor. Nevertheless, only minimal mesangial proliferation was histologically seen in the SCID-SLE mice, and

the absence of significant proteinuria or of azotemia was notable.

EHRENSTEIN et al.<sup>13</sup> showed in a similar model that some human anti-DNA antibodies can deposit in the kidneys and induce proteinuria in SCID mice but in their model again there were no signs of renal abnormal pathology which is the hallmark of the murine and human disease.

To summarize both transgenic and SCID mice studies, B cells producing autoantibodies fulfill some of Koch's postulates, namely that in experimentally induced disease (transgenic/reconstituted mice) the microorganism (autoantibodies) can again be isolated. However, despite some production of autoantibodies, this is only temporary, and does not eventually lead to self-perpetuating autoimmune disease in the healthy recipient.

*Are autoreactive T cells the "pathogenic organism" in autoimmune disease?*

Several disease models have been reported in which autoimmune disease is transferable by T lymphocytes. Although causation of disease in these models would tend to support the role of autoreactive cells according to Koch's postulates, we will show with several examples that this transferability is difficult to reproduce, and occurs only under highly selected conditions.

Experimental allergic encephalomyelitis (EAE) is a disease characterized by mononuclear cell infiltration of the white matter, and motor paralysis. This disease is utilized as a representative animal model for human multiple sclerosis, and can be induced by immunization of genetically susceptible animals to myelin basic protein<sup>8</sup>. It seemed likely that autoreactive T cells are mediators of EAE, as the disease can be transferred by T cells from rats actively immunized to basic protein. Several other autoimmune diseases can be similarly precipitated by CD4 T cell clones, such as autoimmune thyroiditis in mice, and experimental allergic neuritis or uveitis. These experimental diseases are all characterized by oligoclonality of the T cell receptor (TCR), in contradistinction to their human counterparts discussed below. However, these models may not be representative of human autoimmune diseases in several ways:

1) Experimental models do not develop spontaneously, but rather are induced by a particularly strong and perhaps not physiologic antigenic stimulus (purified antigen with adjuvant).

2) Even with such a directed stimulus, animals in most models do not develop a chronic relapsing auto-

immune course similar to the situation in human multiple sclerosis, for example. Rather, the animals in EAE, the common rat parallel, develop a single attack of acute encephalomyelitis, spontaneously recover, and thereby become immune to further induction of attacks.

3) Although the pathogenic T cell lines of EAE were found to be present in the thymus, and capable of responding to specific antigen, in the normal host these cells remain dormant despite their autoimmune potential<sup>32</sup>. This supports the presence of a regulatory factor present in the healthy recipient that does not allow the development of a chronic course, despite the demonstrable presence of the autoreactive clones.

GARCHON<sup>15</sup> reviewed studies examining the presence of TCR oligoclonality in human autoimmune diseases. Contrary to the findings in animals, recent studies do not support the role of specific V $\beta$  genes in multiple sclerosis, rheumatoid arthritis, Graves disease, and Hashimoto thyroiditis. Perhaps even more telling is the recent study by PALIARD et al.<sup>35</sup> regarding the  $\alpha$ ,  $\beta$  T cell receptor repertoire in rheumatoid arthritis patients. Certain V $\beta$  (e.g. V $\beta$ 14) were conspicuously absent in peripheral blood mononuclear cells, relative to synovial fluid cells. PALIARD et al.<sup>35</sup> suggested that this finding signifies the role of a V $\beta$ 14-specific superantigen in the pathogenesis of rheumatoid arthritis. An alternative explanation, however, might be that it is this very lack of V $\beta$ 14 in peripheral mononuclear cells that initiates the autoimmune articular attack.

In other animal models of T cell-induced disease, even a single autoimmune attack is difficult to precipitate. The tight skin mouse model is an autosomal dominant model of inherited skin fibrosis. Adoptive transfer of skin fibrosis to syngeneic recipients is possible by the transplantation of both bone marrow and spleen cells; but this was only possible after irradiation with lethal doses<sup>50</sup>. HOLOSHITZ et al.<sup>19</sup> isolated lines of effector T lymphocytes from rats administered and arthritogenic dose of mycobacterium tuberculosis in complete Freund's adjuvant to induce arthritis in rats. This arthritis model, known as adjuvant arthritis, begins after 10 to 20 days, lasts for 3 weeks, and resembles during the period of acute inflammation human rheumatoid arthritis. Inoculation of the arthritogenic cell line (A2) into rats irradiated with 750 rad led to the development of polyarthritis. However, if the rats underwent 200 rads of irradiation, or none at all – adjuvant arthritis could not be passively transferred, even when the pathogenic T cell clones were given in large numbers.

Much evidence from animal and human experiments supports an immunological, cell mediated basis in the pathogenesis of type I diabetes mellitus. Several

experimentally useful and reproducible models have been developed in animals. Diabetes is never spontaneously observed in unmanipulated rats of the PVG/c strain. However, a combination of thymectomy and sublethal irradiation consistently induced diabetes in female rats of this strain. Even in the non-diabetic rats, mild and focal insulinitis could be seen<sup>37</sup>. Diabetes-prone BB/Wor rats develop diabetes in an incidence of 40–70% in both sexes. BB/Wor rats bred for resistance to diabetes have a cumulative incidence of diabetes < 0.1%<sup>18</sup>. However, when the diabetes-resistant rats underwent single doses of total body gamma radiation (125–600 rads), diabetes was induced in 20%. Similarly, diabetes could be transferred only to the BB/W diabetes-prone rat from BB/W rats with acute diabetes. Simple transfer to nude mice, low incidence BB/W, or from BB/W rats without acute diabetes was unsuccessful<sup>22</sup>.

### Induction of Autoimmunity in the Normal Host

Cyclosporine is a potent immunosuppressive agent, whose principal mode of action is through inhibition of interleukin 2 production. Paradoxically (or perhaps not so), cyclosporine aggravates several autoimmune diseases<sup>39</sup>. When cyclosporine is administered to newborn mice for a few days after birth, the mice subsequently develop several organ-specific autoimmune diseases, with autoantibodies. Autoimmunity was prevented when teated mice were inoculated with adult splenic T cells<sup>42</sup>. MARCOS et al.<sup>26</sup> gave CNA/N mice carrying the *xid* mutation (which protects mice with spontaneously occurring lupus) 800 cGy of total body irradiation, followed by cyclosporine. Clinically, the mice developed a systemic disease including asymmetrical polyarthritis, proteinuria, and immunoglobulin deposits in the kidney mesangium and basement membrane. In addition, these mice had evidence of polyclonal B cell hyperactivity, with antinuclear antibodies and other autoantibodies.

The postulated role of the thymus in the pathogenesis of autoimmune disease is well known. Several lines of evidence support the concept that the normal thymus has a protective role, which prevents the normal host from developing an autoreactive state. OGAWA et al.<sup>33</sup> described a 49 year old woman who underwent complete resection of a thymoma and the adjacent thymic gland. At the time, no evidence of an autoimmune or kidney disorder was present. One year later, she developed arthritis, which led to the diagnosis of SLE with kidney involvement.

PENHALE et al.<sup>36</sup> subjected randomly bred Wistar rats

to combinations of thymectomy and whole body irradiation after weaning. When irradiation was applied without thymectomy, 22% of the rats developed thyroiditis similar histologically to Hashimoto thyroiditis in man. When the rats were subjected to both irradiation and thymectomy, 60% developed thyroiditis and autoantibodies to thyroglobulin.

The normal immune system fails to generate destructive responses against self-antigens. T cell tolerance to self-antigens is possible via 3 mechanisms: clonal deletion, clonal anergy (direct inactivation) and indirect inactivation via suppressor regulatory cells. It has been shown that a functional lack or the removal of the thymus can result in impaired clonal deletion. Neonatal thymectomy led to defective deletion of certain "forbidden" T cell clones, i.e. those with potentially self-reactive T cell receptors. Many strains of neonatally thymectomized mice then develop autoimmune diseases, which support the relationship between failure to delete autoreactive T cells in the thymus to the subsequent development of the autoimmune state<sup>20</sup>.

### Candidate Transferable Protective Factors

#### *Gammaglobulins*

One possible candidate for the postulated protective factor in autoimmune disease is an immunoglobulin, probably IgG, present in the healthy but not in the ill or those predisposed to develop autoimmunity. In recent years, much evidence has accumulated pointing to the diverse and significant therapeutic potential of gammaglobulin (IVIG) therapy<sup>12</sup>. The course of several autoimmune disorders has been modified, often dramatically, by intravenous administration of purified, high dose gammaglobulins (0.4 g/kg for several days). At first, improvements were noted mainly in diseases classically associated with B cell activation. In SLE, hematologic problems were reversed in newborns of mothers with SLE<sup>17</sup>, renal IgG deposits were mobilized concomitant with improved immune function<sup>24</sup>, and a significant decrease in the accumulation rate of recalcitrant massive bilateral pleural effusions was noted<sup>2</sup>. In rheumatoid arthritis, 7 of 10 patients studied by COMBE et al.<sup>9</sup> responded to IVIG derived from human placentas. Also in rheumatoid arthritis<sup>43</sup>, 60% of 31 patients experienced a 50% improvement in disease parameters. These beneficial effects were not noticed when low amounts of IVIG was used<sup>21</sup>. A substantial benefit of high dose IVIG has been also shown in neurologic diseases as dermatomyositis, Guillain-Barre syndrome, and other inflammatory polyneuropathies<sup>10, 16</sup>.

Immunoglobulin therapy was attempted also in

classical T cell related autoimmune disease – adjuvant arthritis. ULMANSKY and NAPARSTEK<sup>49</sup> induced adjuvant arthritis in Lewis rats (a susceptible strain) by vaccination with complete Freund's adjuvant. Rats receiving either human, mice or rat immunoglobulins in doses as low as 10 mg/kg did not develop disease. The injection could be given as early as day 1 or as late as day 11 after vaccination. Despite protection from disease induction, the treated rats had no suppression of their activity to react to the immunizing antigen or to develop resistance to diseases reinduction. Suppressive effect of immunoglobulin therapy was strain specific, and was **not** conferred by immunoglobulins from disease-prone rats, but only from humans or rats from disease-resistant strains. The therapeutic specificity of the immunoglobulin molecule was to the F(ab)<sub>2</sub> portion, but not to the Fc. These results suggest that rats prone to develop adjuvant arthritis are lacking a subset of antibodies present in resistant strains which prevent or suppress disease manifestations in the healthy or resistant.

#### *Glucocorticoids*

Ten to twelve days after immunization with myelin basic protein homogenized in Freund's complete adjuvant, susceptible strains of rats develop EAE, which progresses to urine incontinence and bilateral hind leg paralysis. EAE remits spontaneously after about 5 days, and recovered animals are refractory to attempts to induce further episodes of paralysis. Disease susceptibility is strain dependent, with Lewis rats being most susceptible<sup>27</sup>.

MASON et al.<sup>27</sup> summarized the principal findings when EAE is induced in the rat by purified myelin basic protein:

- 1) The onset of the disease is associated with a large increase in serum corticosterone levels, which remain increased until the disease begins to remit.
- 2) Adrenalectomy of Lewis rats before signs of the disease appears prevents spontaneous recovery. Paralysis becomes progressive, and ultimately fatal<sup>25</sup>.
- 3) If adrenalectomized Lewis rats are given a hormone implant producing corticosterone levels similar to controls, recovery is uninhibited<sup>25</sup>.
- 4) Adrenalectomy delayed until the beginning of the recovery phase does not prevent recovery or the development of refractoriness<sup>28</sup>.
- 5) If PVG rats (a resistant strain) are adrenalectomized and given only basal steroid replacement doses, they lose resistance to disease induction and develop fatal paralysis.

Mason proposes a basic, dynamic balance between cell mediated and antibody mediated immune responses

in the normal host<sup>25</sup>. Glucocorticoids can tip the balance in favor of the latter, and can prevent inappropriate, exaggerated cell mediated immunity responses leading to autoimmune manifestations, as in the EAE model. Put differently, resistance to the induction of autoimmunity and recovery from an ongoing inflammatory process was shown in this model to be dependent on the presence of a protective factor – in this case a glucocorticoid hormone secreted from the adrenal gland.

A single injection of streptococcal cell wall fragments into Lewis female rats induces an arthritis mimicking human rheumatoid arthritis. Histocompatible Fischer rats, however, do not develop arthritis in response to the same stimulus. STERNBERG et al.<sup>44</sup> examined the hypothalamic-pituitary-adrenal axis in these rat strains. In contrast to the Fischer rats, the susceptible Lewis strains had markedly impaired corticotropin and corticosterone responses to corticotropin releasing hormone, interleukin 1, and streptococcal cell-wall fragments. Replacement doses of dexamethasone in Lewis rats markedly attenuated the severity of the arthritis, while treatment of the Fischer rats with a glucocorticoid antagonist led to development of severe inflammatory disease in these previously resistant rats. These data suggest that resistance to autoimmune attack in this model of arthritis is mediated by corticosteroids, and susceptibility to disease in the Lewis rats is due to lack of a factor present in the "healthy" (resistant Fischer rats).

#### *Apoptosis genes*

One of the extensively investigated murine models for SLE is the MRL-lpr/lpr strain. These mice exhibit massive lymphoid proliferation ("lpr" denoting lymphoproliferation), high titer anti-DNA, and early lethal immune nephritis<sup>1</sup>. The work by WANTANABE-FUKUNAGA et al.<sup>51</sup> have contributed to the understanding of the relationship between the lpr gene and the autoimmune phenotype. Fas antigen is a cell surface protein expressed in various tissues including the thymus of normal mice, that is important in the mediation of apoptosis. Almost no Fas mRNA was observed in homozygous lpr mice, due to rearrangement of the structural gene for the Fas antigen. It was postulated that the lpr defect may result in defective negative selection of self-reactive T cells in the thymus, excessive numbers of autoreactive T cells released to the periphery, and autoimmune disease. These findings were expanded by MOUNTZ et al.<sup>31</sup>, who constructed MRL-lpr/lpr mice transgenic for Fas antigen. These mice expressed high levels of Fas in the thymus and T cells, but not in B cells. None of the transgenic mice de-

veloped lymphadenopathy by 4.5 months of age, kidney function normalized and the glomerulonephritis eliminated.

In summary, we suggest that autoimmunity might not be due to the presence of a detrimental element in the autoimmune individual, but rather results from a lack of some protective factor present in the healthy. As we have seen, Koch's postulates as related to autoimmunity cannot be fulfilled with autoantibodies or autoreactive T cells as the pathogenic factor. On the contrary, it seems that these postulates are better applied to what is present in the healthy. We do not think the difference between autoimmunity as the "presence of a pathogenic factor" versus the "lack of a protective factor" is simply a semantic one. Viewing autoimmunity as potentially correctable with elements from the healthy host would dictate more intensive research into potential candidate factors present in the healthy which can be transferred to the sick, and capable of alleviating the autoimmune state.

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