# Natural autoantibodies might prevent autoimmune disease

Irun R. Cohen[1] and Anne Cooke[2]

*Autoantibodies are common in healthy individuals and appear not to be harmful. It is not clear how they arise nor what their function is. Here Irun Cohen and Anne Cooke propose that these natural autoantibodies bind to self or self-mimicking epitopes and so prevent the initiation of a damaging autoimmune response.*

As a corollary to his clonal selection theory, Burnet outlawed forbidden clones of self-recognizing lymphocytes[1]. The logic itself was convincing: autoantibodies, the agents of autoimmune disease, arise as a consequence of self-recognition. Therefore the way to prevent autoimmune disease is to eliminate self-recognition. Although Grabar was quick to propose a physiological role for autoantibodies[2], and some evidence for the existence of self-recognizing T lymphocytes was reported later[3,4], most immunologists believed that autoreactivity was incompatible with health. Hence, many have been surprised by the prevalence of autoantibodies in healthy individuals. It has been shown that normal adult humans and mice, and even newborn mice have B lymphocytes which secrete antibodies recognizing a variety of self-antigens[5–11]. At the Princess Lilianne Foundation meeting on autoimmunity in Brussels, 1985, it was debated whether 30% or 'only' 10% of B lymphocytes in normal, healthy individuals were engaged in producing autoantibodies. Moreover, an entire class of B lymphocytes (Lyb $1^+$ B cells) seems to be involved in making autoantibodies[12]. Thus, rather than a forbidden aberration, autoantibodies appear to be the norm.

This revelation raises questions regarding the function of autoantibodies in disease and in health. First, if we all, the well and the ill, have autoantibodies, when is autoimmunity disease? Disease states cannot be characterized merely by a greater quantity of autoantibodies; persons with very high titers of monoclonal antibodies to self-antigens may have no symptoms of autoimmune disease[13].

It is conceivable, however, that the isotype of the autoantibody could be important in determining its capacity to cause disease. Most natural autoantibodies are of the IgM class while autoantibodies associated with disease tend to be IgG[14]. Thus, an Ig class switch may be critical in the disease process.

A paradigm of autoimmune disease is myasthenia gravis, which has been blamed on autoantibodies to the acetylcholine receptor[15]. Nevertheless, high concentrations of acetylcholine receptor antibodies may be observed in persons without disease[16] and clinical myasthenia gravis may occur with little or no circulating antibody to the receptor[17].

If the role of autoantibodies in autoimmune disease is unclear, the function of autoantibodies in the healthy is puzzling. Holmberg and Coutinho recently have reviewed the problem of natural autoantibodies in the healthy[18]. They proposed that natural autoantibodies are under the strict control of an idiotypic network – a control facilitated by widely shared idiotypes, or 'high connectivity'. According to Holmberg and Coutinho, the threat inherent in naturally autoreactive lymphocytes is tempered by their segregation as an internally controlled set, distinct from the lymphocytes that recognize foreign antigens. This latter set of lymphocytes, less restrained by idiotypic connectivity, is free to respond vigorously to foreign antigens. However, a hypothetical mechanism for the control of natural autoantibodies does not clarify their presence in the first place. Do autoantibodies exist only to be suppressed? In our view, probably not. The

[1]*Department of Cell Biology, The Weizmann Institute of Science, PO Box 26, Rehovot, 76100, Israel; and* [2]*Department of Immunology, The Middlesex Hospital, London, W1P 9PG, UK.*

Immunology Today, vol. 7, No. 12, 1986

Darwinian logic of biology suggests that if we all have them, they are likely to have some intrinsic survival value.

We will argue here that natural autoantibodies may be useful in their own right, that they may help the avoidance of autoimmune disease by blinding the immune system to environmental epitopes cross-reactive with self.

In contrast with endogenous self-antigens, which are usually encountered in a tolerogenic form, self-mimicking epitopes on microbes are usually accompanied by powerful enhancers of the immune response including foreign carrier determinants, adjuvant molecules, products of inflammation, interleukins, and antigen-presenting cells with increased expression of MHC class II genes. Thus, self-mimicking structures on microbes might possibly set off an autoimmune response in the host involving IgG antibodies and effector T lymphocytes. Moreover, self-mimicking epitopes are probably not rare. Complex parasites seem to produce host-like molecules as a strategy for evading host surveillance[19]. Receptors for hormones and enzyme molecules with similar functions in host and microbial parasites are likely to share similar structures. Finally, among the hundreds of potential epitopes present on any of the thousands of macromolecules in a single bacterium there must be epitopes that, by chance alone, will bear some structural similarity to host epitopes. This is demonstrated by the monoclonal antibodies which recognize bacterial antigens as well as mammalian self-antigens like DNA[20] or acetylcholine receptor[21], or the clones of T lymphocytes which recognize both mycobacterial antigens and mammalian cartilage proteoglycan molecules[22]. Thus, the immune response with an enormous repertoire of randomly generated receptors must have ways of avoiding responses to dangerously self-similar epitopes while responding vigorously to adacent, safely foreign structures. We propose that natural autoantibodies could constitute one of the ways.

Although the mechanism of action is not entirely clear, preformed antibodies are powerful agents for blinding the immune system. Their effect has been exploited for years as a standard practice to prevent the development of IgG anti-Rh antibodies in $Rh^-$ mothers who have given birth to $Rh^+$ babies. The administration of preformed anti-Rh antibodies to the mother after delivery prevents her from mounting a vigorous secondary response to the Rh antigens of her next $Rh^+$ foetus *in utero*, sparing the baby erythroblastosis foetalis. As long as each delivery, with its attendant exposure to Rh antigens, is followed by administration of preformed anti-Rh antibodies, the mother's immune system fails to register the experience in its memory. The next exposure to Rh antigen is construed as a first contact.

Is it not possible that the natural autoantibodies may perform a similar function in blinding the immune system to self-antigens and self-mimicking epitopes on microbial invaders? Thus, natural autoantibodies could act as a filter to ensure that only non-self epitopes impinge on the immune system and arouse a violent effector response. Epitopes recognized by preformed natural autoantibodies would be ignored and fail to elicit an aggressive response. The immune response must be focused on only a few of the large number of potential epitopes present on any complex macromolecule[23]. The preformed natural autoantibodies might help ensure that the epitopes chosen for an effector response are not crossreactive with self.

How preformed antibody might blind the immune system is not known: passive blocking of the antigen or active feed-back inhibition would be equally useful in preventing autoimmune disease. How the natural autoantibodies arise is also unclear. However, neither area of uncertainty blunts the thrust of the argument. That the bulk of natural autoantibodies are IgM and have a short half-life in the body suggests that they must be secreted continuously and not sporadically. An idiotypic network, as proposed by Holmberg and Coutinho[18], would do as well as any other mechanism that could generate the production of a continuous pool of IgM autoantibodies. Obviously the delicate job of sorting between self and not-self must be performed by more than one mechanism and suppressor cells, anti-idiotypes, and other factors are probably important. Be that as it may, we all have many natural autoantibodies. Their presence can be understood more readily if they serve some useful purpose.

Irun Cohen is the incumbent of the Maurerberger Professorial Chair in Immunology. Ms Pamela Rubinstein's help in the preparation of this manuscript is gratefully acknowledged.

**References**


1 Burnet, F.M. (1959) *The Clonal Selection Theory of Acquired Immunity,* Nashville, Vanderbilt, University Press
2 Grabar, P. (1983) *Immunol. Today* 4, 337–339
3 Cohen, I.R., Globerson, A. and Feldman, M. (1971) *J. Exp. Med.* 133, 821–833
4 Cohen, I.R. and Wekerle, H. (1973) *J. Exp. Med.* 137, 238–244
5 Guilbert, B., Dighiero, G. and Avrameas, S. (1982) *J. Immunol.* 128, 2779–2787
6 Guilbert, B., Dighiero, G. and Avrameas, S. (1982) *J. Immunol.* 128, 2788–2792
7 Avrameas, S., Dighiero, G., Lymberi, P. and Guilbert, B. (1983) *Ann. Immunol.* 134D, 130–135
8 Dighiero, G., Lymberi, P., Mazie, J.C. *et al.* (1983) *J. Immunol.* 131, 2267–2272
9 Mackay, I. (1983) *Immunol. Today* 4, 340–342
10 Holmberg, D., Forsgren, S., Ivans, F. *et al.* (1984) *Eur. J. Immunol.* 14, 435–441
11 Dighiero, G., Lymberi, P., Holmberg, D. *et al.* (1985) *J. Immunol.* 134, 765–771
12 Stall, A.M., Lalor, T.A., Herzenberg, L.A. and Herzenberg, L.A. (1986) *Ann. Immunol.* 137D, 173–176
13 Shoenfeld, Y., Ben-Yehuda, O., Naparstek, Y. *et al.* (1986) *J. Clin. Immunol.* 6, 194–204
14 Clough, J.D. and Valenzuela, R. (1980) *Am. J. Med.* 68, 80–85
15 Lindstrom, J.M., Engel, A.G., Seybold, M.E. *et al.* (1976) *J. Exp. Med.* 144, 739–753
16 Lindstrom, J.M., Seybold, M.E., Lennon, V.A. *et al.* (1976) *Neurology* 20, 1054–1059
17 Drachman, D.B. (1978) *N. Engl. J. Med.* 298, 136–142
18 Holmberg, D. and Coutinho, A. (1985) *Immunol. Today* 6, 356–357
19 Bloom, B. (1979) *Nature (London)* 279, 21–22
20 Shoenfeld, Y., Rauch, J., Massicotte, J. *et al.* (1983) *N. Engl. J. Med.* 308, 414–420
21 Stafansson, K., Dieperink, M.E., Richman, D.P. *et al.* (1985) *N. Engl. J. Med.* 312, 221–225
22 Van Eden, W., Holoshitz, J., Nevo, Z. *et al.* (1985) *Proc. Natl Acad. Sci. USA* 82, 5117–5120
23 Cohen, I.R., Altmann, D. and Friedman, A. (1985) *Immunol. Today* 6, 147–148