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Unraveling autoimmunity

The immune system can suddenly turn on itself and target its own organs, tissues and cells for destruction: what we call autoimmunity. Most of the more than 70 distinct types of autoimmune diseases are rare, but collectively they affect millions of individuals worldwide. In the USA alone, 5% of the population—over 14 million people—are affected by these debilitating disorders. Although the mechanisms that lead to autoimmunity are still not clear, the past two decades of research on the immune system have yielded rich insights into the pathogenesis of autoimmune diseases. These accomplishments have led to the identification of possible new therapies to treat and even prevent autoimmune diseases.

This issue of *Nature Immunology* brings you up to speed in this fast-moving area with a special Focus on Autoimmunity, from both basic research to clinical results. Included are Commentaries, News & Views and Reviews that cover some of the main areas of research in autoimmunity: therapeutics, genetics, infectious agents and environmental triggers, pathogenesis and animal models. In addition, we have included Round-ups of the most interesting papers on autoimmunity recently published in other journals. Our online Focus on Autoimmunity (http://immunol.nature.com/special_focus/autoimmunity) is free, for the next three months, to all who register; it includes an annotated list of landmark papers that we, and our scientific advisers in the immunology community (see the website), consider to be "autoimmunity classics". Our free-access links to the full text of autoimmunity papers published by the Nature Publishing Group will help you delve even deeper into the world of autoimmunity. The website Round-ups will be frequently updated to keep you abreast of late-breaking developments in the field. Our special thanks go to the Juvenile Diabetes Research Foundation and the American Autoimmune-Related Diseases Association for their sponsorship.

Basic research into the pathogenesis of autoimmune diseases has laid the foundations for new therapeutic approaches to treatment. Fathman's Overview compares and contrasts the determinants for the development of different autoimmune diseases. Steinman, Eisenbarth, Feldmann, Weetman and Lipsky summarize the latest advances in our understanding of multiple sclerosis, diabetes, rheumatoid arthritis, thyroiditis and lupus, respectively, in a series of short News & Views. As pointed out by Fathman, these and other autoimmune diseases are multifactorial in origin, with contributions from genetics, environmental factors and immune dysregulation.

Many autoimmune diseases are linked to the MHC. However, as Wakeland describes in his Review, other gene families are also important in autoimmune disease pathogenesis. Completion of the Human Genome Project should help identify more genes that control autoimmunity and aid the development of low-cost screens to assess an individual's potential risk of developing disease.

Although the role of genetics in autoimmune disease pathogenesis is not hotly debated, molecular mimicry as a trigger of autoimmunity is an area of contention. Many infectious agents are associated with autoimmune diseases, but how strong is the case for mimicry in initiating disease? As discussed by Mathis and Benoist, the potential for T cell epitope mimicry certainly exists, but current evidence is not yet convincing enough. Clearly, this area will see continued activity.

Animal models are commonly used to study the genetic, environmental and pathogenic aspects of autoimmune diseases. In his Commentary, David discusses how useful they are in terms of understanding human autoimmune diseases. For example, animal models have borne out studies in humans that suggest sex hormones are part of the explanation for why autoimmune diseases disproportionably affect women (see Whitacre's Commentary for an in-depth analysis of sex differences in autoimmune diseases). But tolerogenic strategies, such as oral tolerance, that have been effective in many animal models have thus far failed in humans. It remains to be seen whether other tolerogenic approaches, as described by Cooke in her Review, will be relevant in humans.

Regulatory T cells, reviewed by Powrie, participate in maintaining peripheral tolerance. She suggests that this T cell subset could be useful therapeutically, not only in treating autoimmune disease, but also in tumor therapy. However, the relationship between autoimmunity and tumor immunology is complex. As Gilboa discusses in his Commentary, therapy designed to enhance the immune response to tumors risks inducing autoimmune diseases. Conversely, certain autoimmune diseases are linked with development of lymphomas, as Rose reports in his Commentary on a recent meeting that was held to discuss this area. Placing this issue aside, in the past 20 years we have begun to make great in-roads in our understanding and treatment of autoimmune diseases, as highlighted in Martin's Commentary on multiple sclerosis. The ground-breaking work of Erlich and Landsteiner in the early 1900s set the stage for autoimmunity research. Fundamental progress is now being made that will carry us through to the next century. We invite you to read the Focus, visit the website and find inspiration for your contribution to this great effort.