

**michael hertl (ed.)**

# **autoimmune diseases of the skin**

**pathogenesis, diagnosis, management**  
**second edition**



 SpringerWienNewYork

Michael Hertl (ed.)

Autoimmune Diseases of the Skin

Pathogenesis, Diagnosis,  
Management

Second, revised  
and enlarged edition

SpringerWienNewYork

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## Foreword

Based on recent advances in the understanding of the immunological pathogenesis of many chronic inflammatory disorders there is increasing evidence that several of them are characterized and potentially mediated by autoimmune phenomena. Classical examples are rheumatoid arthritis, myasthenia gravis, pemphigus vulgaris, lupus erythematosus and multiple sclerosis. Others, such as psoriasis vulgaris, some less well-characterized collagen vascular disorders, vasculitides and a subtype of chronic urticaria have a more or less pronounced autoimmune background that has to be considered in the overall management of these disorders. A significant portion of autoimmune diseases precipitate primarily or secondarily at the skin. Understanding the cutaneous symptoms may be therefore crucial for the diagnosis, classification and therapeutic management of organ-specific and systemic disorders that require special attention by the physician.

This book is set out to present the most recent scientific and clinically relevant state-of-the-art-knowledge on the broad spectrum of autoimmune disorders affecting the skin. It is meant to provide the most recent information on these disorders for clinicians as well as practitioners in dermatology, medicine, rheumatology, ENT, pediatrics, ophthalmology, orthopedics etc and for basic scientists interested in human autoimmunity. Each book chapter dealing with a distinct cutaneous autoimmune disorder consists of an introduction focusing on the state of knowledge regarding pathogenesis and epidemiology followed by a practical guide how to identify and handle the particular disorder(s). Special attention is paid to genuine cutaneous autoimmune disorders such as autoimmune bullous skin disorders including pemphigus, pemphigoid and epidermolysis bullosa acquisita. These disorders can be considered as paradigms of organ-specific autoimmune disorders because autoantigens and autoantibody-mediated pathogenesis are well-characterized.

Major progress has been made in the diagnosis and classification of collagen vascular disorders such as systemic sclerosis, lupus erythematosus, dermatomyositis and overlap syndromes. These advances have provided the basis for more specific therapeutic interventions. Recent pathogenetic findings in psoriasis, lichen planus and chronic urticaria have led to novel therapeutic concepts that will replace the "classical" symptomatic treatments that have been established for decades. One striking example is the therapeutic effect of biologics in severe psoriasis vulgaris and psoriatic arthritis and the

modulatory effect of high dose immunoglobulins in dermatomyositis and severe vasculitides. In addition to the book chapters on distinct clinical cutaneous disorders, the introductory chapter explains basic immunological principles leading to autoimmunity and the final chapter gives an overview of the mode of action of novel immunomodulatory drugs. The present book which is edited by my co-worker Dr. Michael Hertl is set out to combine major scientific advances in the understanding of autoimmunity with the clinical presentation and management of these disorders. I am convinced that the book constitutes a very successful effort to provide a handbook for those who are scientifically or clinically interested in autoimmune disorders of the skin. I wish the editor and the authors success with this endeavor.

Erlangen, July 2001

*Gerold Schuler*

## Preface to the First Edition

Hundred years ago, Paul Ehrlich speculated whether an individual is able to produce toxic autoantibodies and about the implications of such antibodies for disease. The contention that an alteration of the body fluids causes disease followed the traditional teachings of Hippocrates and Galen that disease results from dysfunction of the four humors. However, Ehrlich introduced the novel concept of antigen specificity that was based on his side chain theory of antibody formation: (1) antibodies are naturally occurring substances that serve as receptors on the cell surface; (2) the specificity of antibody for antigen is determined by a unique stereochemical configuration of atoms that permits the antibody to bind tightly and chemically to its appropriate antigen; (3) the number of different combining sites structures available is so great that each one differs from the others, with little or no cross reactivity among them; (4) and in order to induce active antibody formation, it is only necessary that appropriate receptors be present on the cells for antigen to interact with them and so stimulate their overproduction and liberation into the blood. According to this description by Paul Ehrlich, the antibody appeared to be a polymorphous cytoplasmic agent with a unique feature – a highly organized combining site (the haptophore group) that determined its unique antigen specificity.

It was Bordet who showed that anti-erythrocyte antibodies were capable of mediating immune hemolysis giving rise to the idea that self-produced hemolytic antibodies might assist in destroying autologous erythrocytes.

This and similar findings including the description of cytotoxic antibodies against a variety of other cell types prompted Ehrlich to say: "... the organism possesses certain contrivances by means of which the immunity reaction, so easily produced by all kinds of cells, is prevented from acting against the organism's own elements and so giving rise to autotoxins ... so that we might be justified in speaking of a 'horror autotoxicus' of the organism. These contrivances are naturally of the highest importance for the individual" (P. Ehrlich and J. Morgenroth, Berlin. Klin. Wochenschr., 1901).

When Metalnikov was the first to demonstrate the generation of autoantibodies that were cytotoxic against spermatozoa *in vitro*, Ehrlich questioned that they were able to induce pathology *in vivo*.

It took, however, more than forty years that some distinct organ-specific immune disorders were categorized as true autoimmune diseases. Among the first identified were autoimmune orchitis, allergic encephalomyelitis, autoimmune

thyroiditis, pemphigus vulgaris and bullous pemphigoid. Noteworthy, some of these disorders are exclusively mediated by circulating autoantibodies such as the hemolytic anemias, thrombocytopenia, pemphigus, and pemphigoid while others, such as allergic autoimmune encephalomyelitis and autoimmune thyroiditis require the transfer of immunocompetent cells in addition to autoantibodies.

The existence of immunological tolerance was the logical consequence of Paul Ehrlich's postulate that there was a "horror autotoxicus" a mechanism that inhibited formation of potentially harmful autoantibodies to self *in vivo*. It was Owen to show that dizygotic calves whose circulation was connected *in utero* were unable to respond to each other's antigens after birth. Out of this and similar observations, the clonal deletion theory was invented by Burnet meaning that antigen present during embryonic life would somehow cause destruction of self-reactive clones. The observation that adult animals could be rendered unresponsive to foreign antigens by the administration of large doses of the antigen led to the notion that immunological tolerance could be also acquired.

The recognition of different central and peripheral immune mechanisms leading to immunological tolerance are all based on Ehrlich's concept of "horror autotoxicus", *i.e.* acquired or active immune regulation of unwanted immune responses against self. The finding that B lymphocytes generally require the help of T lymphocytes in their antibody response to a defined antigenic stimulus led to the discovery of distinct immune cell subsets including helper cells, cytotoxic cells and regulatory cells. The identification of the idiotype-anti idiotype network was born out of the discovery that the antigen binding site of the antibody itself can act as an antigen for anti-idiotypic antibodies. Anti-idiotypic immune responses are part of the physiological immune surveillance aimed at limiting the extent of an immune response.

The identification of different lineages of antigen presenting cells has taken away much attention from T lymphocytes as the exclusive regulators of immune and autoimmune responses. Major interest has recently focused on dendritic cells, bone marrow-derived antigen presenting cells with potent capacity to induce primary T-cell-mediated immune responses. However, accumulating evidence has demonstrated that the dendritic cell system bears much more plasticity than originally thought. Dendritic cells can arise from several different types of progenitor cells and different functional types of dendritic cells can be generated from the same precursor. It thus appears that dendritic cells have the potential to modulate immune responses within the wide spectrum of immunity on the one hand and immunological tolerance on the other hand.

The rapid development of immunological research has also provided major insights in the pathogenesis of autoimmune disorders which has implications for classification, diagnosis and therapy of these disorders. Classical examples for well-characterized autoimmune disorders are myasthenia gravis, pemphigus vulgaris, and hemolytic anemia. Furthermore, the availability of recombinant forms of the major autoantigens of these disorders has



provided critical tools to investigate autoimmunity versus immunological tolerance to these self proteins in affected patients and healthy individuals.

The increasing understanding of the mechanisms that lead to immunological tolerance to self and the role that HLA and non-HLA alleles play in antigen recognition by autoaggressive T cells may also lead to novel therapeutic strategies. Several clinical studies have sought to restore immunological tolerance to self by the administration of modified self peptides, such as the administration of altered peptide ligands of myelin proteins in multiple sclerosis. Immature dendritic cells hold great promise as highly efficient tools to induce immunological tolerance to defined self proteins or peptides as demonstrated in murine allograft rejection models. They may induce tolerance by inducing antigen-specific anergy of autoreactive T cells and/ or by the induction of regulatory T lymphocytes that inhibit the activation of autoaggressive T cells.

I am very grateful that internationally leading experts in the field of cutaneous autoimmune disorders spontaneously agreed to provide comprehensive and well-illustrated overviews of the major autoimmune disorders of the skin. It was truly fun to interact with all of them! In addition, I would like to acknowledge the support and efforts of Springer Verlag in making this kind of book possible. We hope that the concept of this book will indeed help to broaden the understanding of cutaneous autoimmune disorders for those working in the many clinical disciplines which are involved in the care of these patients. Finally, I thank my wife for her continuous support and her help and criticism during the development of this book.

Erlangen, July 2001

*Michael Hertl*

## **Preface to the Second Edition**

Thanks to the positive reception of the first edition of the book by the medical community both in Europe and in the USA, the present book has come to its second edition. All the chapters have been thoroughly revised and two new chapters on Vitiligo and Alopecia areata were included.

We hope that the present book will continue to provide state-of-the-art knowledge for those who are interested and clinically involved with autoimmune disorders of the skin.

The present edition of the book is dedicated to my clinical teacher, Professor Gerd-Klaus Steigleder, on the occasion of his 80th birthday.

Marburg, January 2005

*Michael Hertl*

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