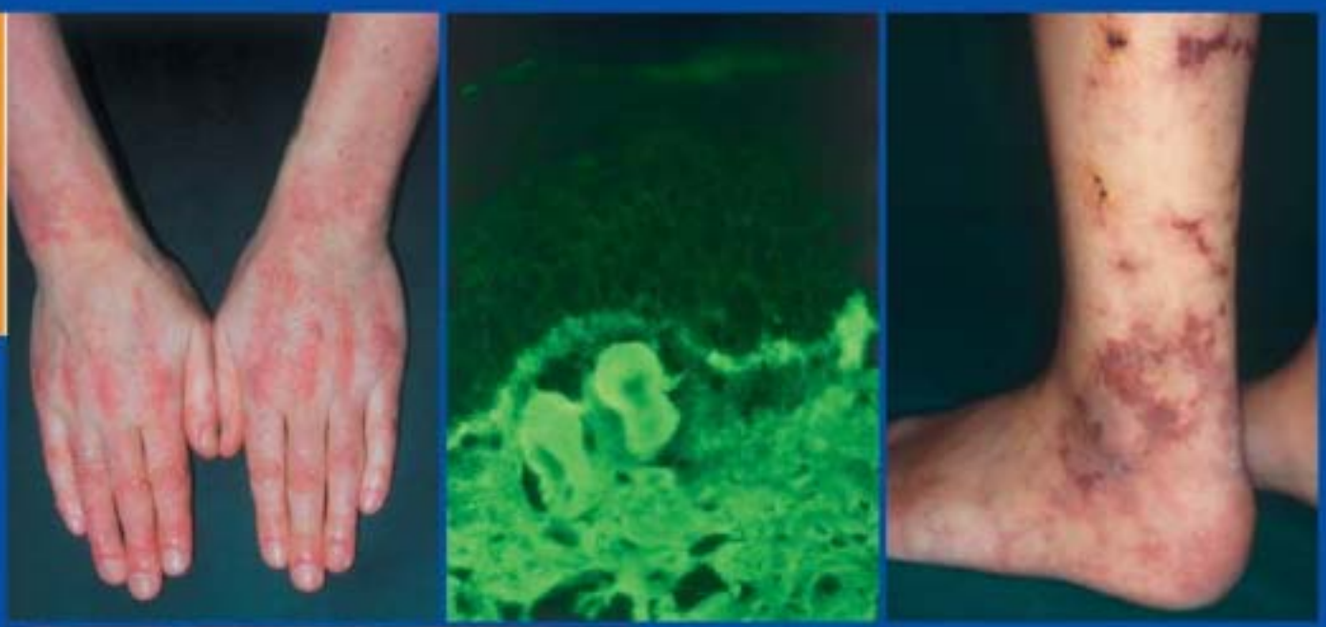
Michael Hertl *Editor*

Autoimmune Diseases of the Skin



Pathogenesis, Diagnosis, Management

3rd Edition

SpringerWienNewYork

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Michael Hertl (ed.)

Autoimmune Diseases of the Skin

Pathogenesis, Diagnosis, Management

Third, Revised and Enlarged Edition

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Front Cover: Systemic lupus erythematosus (A) with subepidermal cytoid bodies and positive lupus band test in lesional skin (B), subacute lupus erythematosus (C) and livedo vasculopathy (D).

Printed with financial support of
Biotest AG
Dreieich, Germany

Printed in Austria
SpringerWienNewYork is a part of Springer Science+Business Media
springer.at

Cover Design: WMXDesign GmbH, Heidelberg, Germany
Typesetting: le-tex publishing services GmbH, Leipzig, Germany
Printing and binding: Theiss GmbH, St. Stefan, Austria

Printed on acid-free and chlorine-free bleached paper
SPIN: 12550098
Library of Congress Control Number: 2010932332

With 95 colored figures

ISBN 978-3-211-99224-1 SpringerWienNewYork
ISBN 978-3-211-20686-8 2nd edition SpringerWienNewYork

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 practicioners 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 autoimmmune 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**

Prefaces

Preface to the Third Edition

We are very grateful for the continuous positive reception of the book which led to the present, third completely revised and enlarged edition of Autoimmune Diseases of the Skin". The contents of the book reflect the rapid development of medical research and its impact on novel diagnostics and treatments in the field of autoimmune disorders.

The third edition of the book is dedicated to my father, Prof. Dr. Michael Hertl, who has been a devoted and most enthusiastic genuine clinician scientist all over his life. His never-ending broad interest to learn and extend his sight of the world has been the driving force for me to join the world of academic medicine.

Marburg, October 2010 **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**

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 Hipppocrates 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 occuring 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 ap-peared 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 fourty 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 idiotypeanti idiotype network was born out of the discovery that the antigen binding site of the antibody itsself 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 antigenspecific 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 continous support and her help and criticism during the development of this book.

Erlangen, July 2001 **Michael Hertl**

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Pathogenesis of Autoimmune Diseases

1

Martin Röcken and Tilo Biedermann

Autoimmunity and autoimmune disease

The term autoimmunity signifies the presence of specific memory-type immune reactions that are directed against one or more self-epitopes. Under most conditions, autoimmunity is determined in terms of immunoglobulins that react with either unknown or well-defined human antigens. Today it is supposed that the production of these autoantibodies requires prior activation of potentially autoreactive B cells by memory T cells. These T cells must not only recognize a closely related peptide structure. Importantly, these T cells can stimulate B cells only when primed by activated antigen presenting cells.

Autoimmunity is a relatively frequent event. Most likely, any individual raises immune reactions against numerous self antigens. This autoimmunity leads only very rarely to overt autoimmune disease. Therefore, the development of autoimmune disease requires trespassing of a large number of additional security levels, beyond autoimmune reactivity (Schwartz, 1998). This is illustrated by two frequent clinical phenomena: One of the best examples are antinuclear antibodies (ANA), which are found in even more than 50% of the female population older than 50 years. Compared to this frequency, ANA-associated autoimmune diseases are relatively rare and affect less than 2% (Rubin, 1997). The other is that only very few autoimmune diseases progress continuously. Most of them progress during short waves of disease activity and in between these waves have long periods of quiescence. Since autoreactive T and B cells do normally not disappear during these periods of quiescence, a series of control mechanisms protect from manifest autoimmune disease.

T and B cells

T cells are small lymphocytes that are characterized by their antigen recognition structure, the T cell receptor (TCR). According to the current state of knowledge, the TCR is only functional as a cell bound structure. Due to the low affinity for free peptide (Weber et al., 1992), the TCR recognizes only antigens that are presented by major histocompatibility complex