

Skin Immune System (SIS)



一九九二年十二月二日

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0008 4437



CRC Press, Inc.
Boca Raton, Florida



Library of Congress Cataloging-in-Publication Data

Skin immune system (SIS) / [edited by] Jan D. Bos.

p. cm.

Bibliography: p.

Includes index.

ISBN 0-8493-4945-1

1. Skin--Diseases--Immunological aspects. 2. Skin--Immunology.

I. Bos, Jan D.

RL97.S65 1989

616.5'079--dc20

89-10022

CIP

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Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida 33431.

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International Standard Book Number 0-8493-4945-1

Library of Congress Card Number 89-10022

Printed in the United States

PREFACE

The number of publications including monographs and edited multi-author volumes, as well as major reviews dealing with the subject of immunodermatology has increased exponentially during the past 10 years. Many textbooks begin with a brief outline of general items such as immunoglobulin structure and synthesis, T and B cells, antigen presenting cells, mediators of inflammation, and immunogenetics, followed by a number of chapters describing the immunopathology of individual diseases. Thus, the main attention within immunodermatology is directed to the way in which immunological mechanisms may be operative in skin disease. One might also say that there is a prominent attention to nature's immunological experiments with human skin that manifest as dermatological disease.

In this book, a different approach was chosen. The present state of knowledge of especially the immunophysiology of the integument is placed centrally throughout the volume. From a pure description of the many and diverse cellular and humoral constituents of the skin immune system onwards, the dysregulations and faults in function leading to loss of homeostasis are described, emphasizing their diversions from the immunophysiological state. It is expected that the concept of completeness incorporated in the denomination SIS will positively influence future investigations both in the physiology and the pathology of the skin. This book is aimed at serving as a primary, bringing in one volume a variety of facts and visions that are otherwise only obtainable from a wide array of different scientific sources.

The stimulating environment within our Academisch Medisch Centrum in Amsterdam, which serves both as the home for the Faculty of Medicine of the University of Amsterdam as well as for the Academic Hospital of the University, was a prerequisite for me to be able to edit this book as well as to serve as co-author of a number of chapters. The fruitful discussions and cooperation between co-workers of especially the Departments of Dermatology, Cell Biology and Histology, and Pathology, some of them being contributors to this book, was essential. In this respect, I especially wish to thank my co-worker and friend, Martien L. Kapsenberg, who was the co-author of the 1986 review on the skin immune system in *Immunology Today*, in which the concept of SIS was first described. Many scientists in the Academisch Medisch Centrum have helped in editing by deliberately functioning as referees for a number of chapters. My teacher in immunodermatology, who was internationally recognized as a major contributor in the field, the late Rudi H. Cormane, agreed with the idea of a multi-author book on the skin immune system and stimulated me to begin with inviting participants. The relative ease by which the many contributors from outside our Centrum accepted the proposal to become a contributor is highly appreciated. All contributors are gratefully acknowledged for their efforts which made the present volume a complete primer for the immunophysiology and immunopathology of the integument.

The technical and secretarial assistance of Suze Krieg, Monique van Rosmalen, Margaret van Nierop, Inge van Rossum, and Robert Rodenburg, as well as the expert artistic contributions of Inge Oosterling are gratefully acknowledged. The editorial assistance provided by Marsha Baker, Rosi Larrondo, and Kristen Peterson of CRC Press was another prerequisite, without which the book would never have come to be published.

Lastly, I would like to thank my dermatological colleagues as well as the residents of the Department of Dermatology, who took much effort in continuing day-to-day care for patients, enabling me to maximally invest time in the composition of the present volume.

Jan D. Bos
February 1989

FOREWORD

Our understanding of the normal physiology and pathophysiology of skin has greatly advanced over the past many years. Much of this progress can be attributed to major advances in knowledge relating to fundamental immunological mechanisms. It has long been known that the skin is a target for many types of immunological disease. In the case of autoimmune blistering diseases, we know from the classic studies of Jordon and Beutner that the skin is a target for antibody-mediated assaults. Their discoveries, as well as those of Cormane in lupus erythematosus and other connective tissue diseases, were indeed pivotal in leading so many clinicians to careers in investigative dermatology, particularly into the special area of immunodermatology. The skin is also a target for immunological assault in other immune-related skin diseases such as leukocytoclastic vasculitis, connective tissue disease, urticaria and angioedema, atopic and contact dermatitis, and drug eruptions. For many of these diseases, we still do not know which unique constituents in skin play a critical role in the generation of these reactions, although the pathomechanisms of some of these diseases are currently under intense study. Recent advances in tissue culture, including utilization of cell-specific growth factors, enable cultured endothelial cells, epithelial cells, as well as mast cells to be used in functional assays which should allow us to address these questions in greater depth.

In addition to serving as a target for immunological assault, the skin can now be viewed as containing its own "immune system". This concept is derived from the enormous number of studies which have identified an immunological role for constituents of the dermis and epidermis. Within normal dermis there are several cells which play potentially critical roles in inflammatory and immunological reactions. Lymphocytes and monocytes, which are continuously percolating through normal skin, are prototypical cells which play pivotal roles in the immune system. As well, mast cells are filled with inflammatory mediators which are either stored or rapidly synthesized in response to various signals. In recent years, numerous studies have indicated that endothelial cells may also play an important role in inflammatory skin reactions by exhibiting immunologically relevant cell surface molecules in response to certain stimuli as well as by elaborating proinflammatory cytokines. These cells of the dermis, independently or through interactions with other cells or their products, are presumably crucial in eliciting varied skin reactions.

Another important component of the skin's immune system is the epidermis, which is also a heterogenous organ. Four or in some (murine) species five different cell types reside within the epidermis. Langerhans cells are bone marrow-derived dendritic cells which reside within the epidermis and, although they represent only 3 to 4% of all epidermal cells, they exhibit many important accessory cell and antigen presenting functions. Over the past 10 years these and other important immunological characteristics of Langerhans cells have been identified. Furthermore, since they are so superficially situated their functions are subject to the modulating effects of numerous physical and chemical agents which may be applied to the skin. In addition to Langerhans cells, other cells within the epidermis play a critical role in the generation, perpetuation or down-regulation of immunological and inflammatory reactions. For example, keratinocytes, which comprise the major subpopulation of epidermal cells and which were thought to be immunologically irrelevant until a few years ago, have been shown to secrete numerous cytokines which have a broad range of biological activities. Through molecular biological techniques, the chemistry of these cytokines is being defined, and in the next few years with the use of recombinant DNA, the *in vivo* functions of these cytokines will hopefully be defined. In addition to the production of cytokines, keratinocytes can potentially participate in immune responses via their synthesis and expression of class II major histocompatibility complex antigens in response to γ interferon which is presumably produced when activated helper T cells infiltrate the skin. This phenomenon, however, is complicated since *in vitro* studies indicate that these class II positive keratinocytes do not serve the same functions as do

class II positive Langerhans cells. Enhancement of T cell attachment, facilitation of Langerhans cell migration, and induction of immunological unresponsiveness are three not mutually exclusive hypotheses which have been advanced for the role of these class II bearing keratinocytes. Finally, until only a few years ago, the Thy 1+ dendritic epidermal cell was unknown. Since its discovery there has been a fervor of activity in elucidating the ontogeny and function of these bone marrow-derived cells. Molecular biological studies have indicated that they are immature T cells. The human analogue of this cell has not been identified, although further study may identify similar cells within human epidermis.

In the study of immunodermatology, it is clear that immunologists interested in many fundamental immunological processes have come to utilize the skin no longer just because of its easy access, but for its intriguing possibilities with regard to its rich source of immunologically important constituents and because of the many still incompletely understood inflammatory and immunological diseases affecting the skin. The contents of this book, which summarize as well as indicate new directions for research in immunodermatology, attest to the reality and importance of the "skin immune system".

Stephen I. Katz
March 1989

THE EDITOR

Jan D. Bos, M.D., Ph.D., is Associate Professor of Dermatology in the Faculty of Medicine of the University of Amsterdam, The Netherlands, and vice-chairman of the Department of Dermatology, which is seated in the Academisch Medisch Centrum in Amsterdam.

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Dr. Bos is an active member of the European Society for Dermatological Research, The Netherlands Association for Dermatology and Venereology, and the Dutch Society for Immunology. He serves on many faculty committees, as well as on several committees of the Netherlands Association for Dermatology and Venereology. He has presented his research work at many international meetings and is regularly invited as a speaker and as a chairperson during international symposia, seminars, and congresses. He has published over 75 papers and chapters in books. His current research interests are in the immunophysiology of human skin, immunopathology of psoriasis, atopic dermatitis and other common skin disorders, as well as AIDS, and in the application of new immunosuppressants such as the cyclic peptides in clinical dermatology.

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PART I:
INTRODUCTION

PART I
INTRODUCTION

Chapter 1

THE SKIN IMMUNE SYSTEM (SIS)

Jan D. Bos, Pranab K. Das, and Martien L. Kapsenberg

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