# Immunodermatology

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# Comprehensive Immunology

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*New York, New York*

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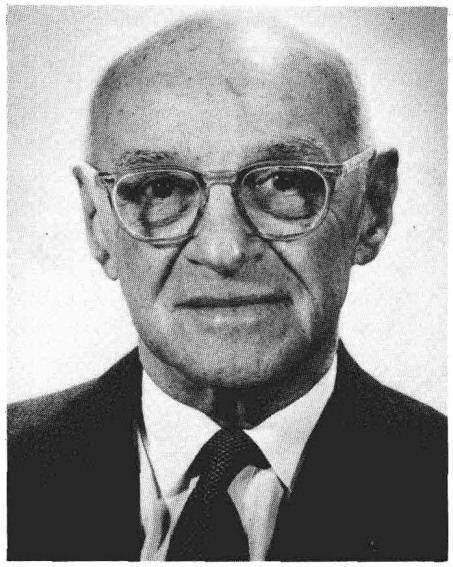
*We dedicate this book to Marion B. Sulzberger, teacher, investigator and humane physician, in recognition of his fundamental contribution to dermatology and immunology for more than fifty years.*



MARION B. SULZBERGER, M.D., F.A.C.P.

Dr. Marion B. Sulzberger was born on March 12, 1895, in New York City. He attended Harvard and then went on to the University of Zurich where he received his medical degree in 1926. He was the first George Miller MacKee Professor of Dermatology and Syphilology at New York University (1955–1969), where he is still Professor Emeritus. He has been a Clinical Professor of Dermatology at the University of California at San Francisco since 1961 and is also President of the Institute for Dermatologic Communication and Education.

Dr. Sulzberger has had a long scientific career in which he contributed much original work. During this time he accomplished the following:

Described "Incontinentia pigmenti" with Dr. Bruno Bloch (1928).

First demonstrated specific immune tolerance in laboratory animals (in guinea pigs with neoarsphenamine) (1929).

Introduced the patch test into the United States with Dr. Fred Wise (1931).

Coined the term "atopic dermatitis" with Dr. Arthur Coca and delineated the clinical and immunological aspects of the syndrome (1932).

Demonstrated that certain vascular ill effects of tobacco are based on allergic response rather than due to nicotine (1934).

Described the distinctive exudative, discoid, and lichenoid chronic dermatosis with Dr. William Garbe (1937).

Carried out the first experimental sensitization with DNCB of human skin in the United States, with Dr. A. Rostenberg (1939).

Demonstrated the connection between miliaria, the sweat retention syndrome, and tropical anhidrotic asthenia with Dr. Franz Hermann, Harry Zimmerman, and co-workers (1946).

Perfected the method of simultaneous, symmetrical, paired comparisons for assaying the relative effects of topical agents (with collaborators) (1947).

Introduced the therapeutic efficiency of topical steroids in inflammatory dermatosis with Dr. Victor H. Witten (1952).

Demonstrated the effectiveness of occlusive dressings (Saran Wrap) in enhancing therapeutic effects of topical medicaments with Dr. Victor H. Witten (1960).

Demonstrated the mechanism of friction blistering, its pathology, its physical and chemical changes, and methods of prevention and management at Letterman Army Institute of Research with collaborators (1966–1969).

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# Foreword

By 1940, immunological mechanisms had been proved to have fundamental influences on a great number and variety of skin reactions, and skin diseases had brought to light a great number of fundamental immunological mechanisms that were basic to a wide range of different diseases, dermatological and nondermatological. The preeminence of dermatological research in the advancement of immunological knowledge should not astonish anyone. For the skin is not only the most easily accessible tissue for producing and studying immunological reactions, it is also the great organ of protection that meets the first onslaughts of inimical environmental forces and agents—potential enemies, both living and dead. And protection is in essence what immunology is all about.

To get an idea of the long-established role that testing the skin and the study of its many reactions has played in advancing general immunology, one need recall only smallpox vaccination; tuberculin testing; testing with fungal extracts; skin testing in hay fever, asthma, and serum sickness; skin tests with toxins and toxoids; the patch test; the passive transfer of skin-adhering antibodies (reagins); skin sensitization by simple chemicals; and similar dermatological procedures that have exerted their influence on medical and scientific disciplines far beyond dermatology.

But these older tests and observations were only the forerunners of the present complexities of immunodermatology—the permutations of the interactions between different varieties of T cells and B cells; the Langerhans cell; the transfer factor; the immunodeficiencies; the complement cascade and complement deficiencies; the opsonins; the phagocytic mechanisms; the autoantibodies; the enzymes and chemical mediators; and the legion of other immunological phenomena that play their parts in skin reactions and diseases.

The speed at which knowledge about the immunology of the skin has grown in the past few decades is such that a practitioner of medicine can hardly be successful and a research worker in immunology can hardly be productive without acquaintance with the advances in immunodermatology. Therefore, this text on immunodermatology, encompassing the latest advances in this branch of science, satisfies an absolute need of both practitioners and investigators.

Over 300 years ago, Hermann van Boerhaave, the great physician of Leyden, made the following pronouncement: "Simplicitas sigillum veritatis" (Simplicity is the sign of truth). Nothing could be further from the truth in regard to immunodermatology today. For such are the complexity and scope of modern knowledge about the immunology of the skin that the present textbook has achieved its remarkable comprehensiveness by drawing on the special expertise of over 60 authorities on particular subdivisions of immunodermatology.

There is about as much resemblance between the dermatological allergy* of 1940 and dermatological allergy today as there is between a newborn baby and a

healthy youth of 18 years. Yet an 18-year-old youth still has a long way to go to achieve the full realization of his promise.

I feel that this is true of the immunodermatology of today. It is like a vigorous youth. For it is just beginning to feel and to exercise its powers. If I am not mistaken, immunological investigations of the skin have before them an era of productivity that will lead to as yet undreamed of successes in the prevention and management of disease. The editors and authors of the present text will have contributed in no small measure to many of these successes.

Marion B. Sulzberger

*I use "dermatological allergy" as a synonym for "dermatological immunology" and for "immunodermatology," also. For me, the term "allergy" means what von Pirquet intended it to mean when he coined it. Allergy covers all acquired specific alterations in the capacity to react in whatever manner and in whatever direction—toward increased sensitivity or susceptibility, or toward decreased sensitivity, decreased susceptibility, or immunity. This makes the science of allergy the equivalent of the science of immunology, in today's usage.

# Foreword

The dawn of immunology in dermatology is traceable to 1940, when Sulzberger published his volume of didactic lectures on *Dermatologic Allergy*. In the preface to that classic book Sulzberger begged his readers "to remember that the study of allergy is very young, and that the careful analysis of any series of facts must lead one almost immediately to the borders of the unknown. It is therefore not astonishing that this new and stimulating brand of medicine should be characterized by rapid progress and by the consequent conflict between old concepts and new findings." Reading this statement today, one realizes its prophecy: never before in the history of medicine has so much information come to light in the short span of 40 years. And no other specialty is so important to dermatology today as immunology.

Skin is a uniquely practical organ for studies on allergic events. It is easily accessible and technically expedient, and has long been favored by clinicians and scientists for investigations ranging from allergic diseases to homografts. Because of gross differences in the timing and the qualitative appearance of test responses to various allergens, skin is a convenient indicator of allergic states and essential in the classification of allergies.

Many allergic diseases that do not normally express themselves in skin can be detected by skin test responses; others produce pathological changes or lesions in the skin secondarily. Still other allergic conditions whose expression is restricted to skin can actually be initiated by normal or altered components of the skin acting as antigens.

A monograph on immunodermatology is timely. An earlier attempt was published in 1969 as Volume XI of the *Advances in Biology of Skin*. At that time, immunologists, dermatologists, and biologists reviewed ahd discussed the status of knowledge of the "roles" played by the skin in the genesis and expression of immunological phenomena. An attempt was made to distinguish between roles unique to skin because of its position, anatomy, and biological constitution and roles that can be or are undertaken by other tissues but that may escape notice.

The present volume is testimony to the great strides made in the science of immunodermatology: our knowledge of the immunopathogenic mechanisms involved in many cutaneous disorders has suddenly exploded. The many chapters in this volume show that the cutaneous system is unique among other organs in that, as a field of study, it represents an ideal union of clinical and academic research.

This publication is the result of the efforts of B. Safai and R. A. Good, two of today's outstanding investigators of clinical and experimental immunology. The book, a thorough review and analysis of skin immunology today, leaves out nothing important, from historical highlights to current understanding, from unsolved problems to the way to future explorations. All of its contributors have

distinguished careers in experimental and clinical dermatoimmunology. Many of them are young enough to have developed *pari passu* with this new science.

This book is unique in its completeness and timeliness. Anyone wishing to be informed on the subject, whether clinician or experimenter, will want a personal copy. For the practicing clinical dermatologist, it is a must.

William Montagna

# Preface

If one could relive history, surely no moment would be more thrilling than when Edward Jenner connected prior exposure to cowpox, among the English milkmaids, with their safety from the smallpox which was scarring, blinding, and killing people throughout eighteenth-century Europe. At that moment, the smooth, healthy complexions of these women became eloquent statements of a saving truth. If Jenner's insight can be said to mark the birth of immunology as a modern medical science, it surely establishes the vital link between immunological changes and the organ which is quickest to reveal them: the skin.

In return for the contributions of the skin to the development of immunological analysis, immunological analysis has radically altered the nature of dermatology, creating a powerful new focus on disease processes which have long been obscure. In recent years, technological advances have made this reciprocal relationship an ever closer one.

The purpose of this book is to present a range of information—basic scientific and clinical, historic perspectives, and sharply defined recent studies—which maps out the present state of immunodermatology. The first chapters establish the overall scientific context in which our work takes place. A second group describes the systems—cellular, genetic, physiological—which furnish the microenvironment for immune processes. The mechanisms of inflammation, as they manifest a wide range of immunodermatological events, are then explored in some depth. Next, three articles on autoimmune disorders introduce a series of papers on specific disease entities, involving the skin, in which the immune system is compromised. Herpes infections, malignancies, and immunodeficiencies are among other diseases examined. The roles of trace metals in cellular and serologic anomalies are among the leads being followed toward greater biological understanding of these processes. The concluding chapters consider the problem of environmental influences and possibilities of broad-based therapeutic approaches.

We hope that this volume will serve as a resource, offering comprehensive background as well as important case studies, and providing a useful tool for the new surge of work in immunodermatology which we have seen to be already in vigorous progress.

Bijan Safai
Robert A. Good

# Introduction

BIJAN SAFAI and ROBERT A. GOOD

Ancient records show that the relationship between the skin and immunological events has been understood for centuries: long before inoculation was performed in England, standard medical practice in China and Turkey featured the inhalation of particles from crusts of healing smallpox skin lesions. Since Edward Jenner's time, the remarkable advances of immunology as a discipline have been consistently marked by use of the skin as a resource. Patch tests and subcutaneous or intradermal tuberculin tests have been in use since the late nineteenth century, and inhalant antigens had been shown to cause immediate urticarial skin reactions as early as the 1860's (Baer, 1976). The potential of an immunogen either to increase or decrease sensitivity, or both—the seeming paradox which was to bring inoculation to the world—was described by Von Pirquet after his brilliant studies of skin reactions (Von Pirquet, 1911). Prausnitz and Küstner's bold experiments, utilizing the concept of passive immunization, made use of Prausnitz's own skin, which gave an urticarial reaction to boiled fish protein after an injection of serum from the originally hypersensitive Küstner (Prausnitz and Küstner, 1921). In their extraordinary studies interpreting this beautiful experiment of Nature, these early clinical investigators discovered desensitization, perhaps today better considered immunization against immunity. They also discovered that certain antibodies, later to be called reagens, adhere firmly to cells in the skin. In the past two to three decades innumerable experimental skin grafts, revealing host-versus-graft reactions, have clarified the role of genetics in allograft rejection and immunological tolerance. As a constant reminder of the association which has brought such benefits to humanity in this century, every summer we see the faint circles left by the tuberculin vaccination on the skin of people's upper arms. And meanwhile, Jenner's work has been completed: the scourge of smallpox has been virtually eliminated from the globe.

We have also found that the association between skin and immunology is reciprocal; studies and discoveries in immunology have greatly affected the state of dermatology. Atopic dermatitis was associated with reagenic hypersensitivity as early as 1923 (Coca and Cooke, 1923) but the lack of distinct diagnostic indicators hindered both research and treatment (Hanifin, this volume). Today we can identify several immunological changes which correlate with the degree of skin involvement in this disease. IgE production is elevated in over 80% of patients with atopic dermatitis, and the highest levels occur in patients with the most severe disease. This imbalance may be due to impaired T-cell regulation (Tada *et al.*, 1973). Increased susceptibility to cutaneous viral, fungal, and bacterial infections poses a serious problem for these patients. The exact nature of the impairment in cell-mediated immunity which underlies this troublesome disorder—whether a

local breakdown in cellular performance or a more general defect of immune cells —has not yet been established.

In Sézary syndrome, an exfoliative dermatitis with intense pruritis, characteristic abnormal T lymphocytes with highly convoluted nuclei which are present in peripheral blood infiltrate the skin (Zucker-Franklin, 1976). Recently it has also been discovered that both this disease and the closely related mycosis fungoides feature increased levels of circulating factors similar to those secreted by thymic epithelial cells (Safai *et al.*, 1979). Evidence that the abnormal T cells of Sézary syndrome preferentially infiltrate the skin, possibly conferring a thymus-like function on the skin itself, suggest a unique relationship between these two organs in this disorder.

Components of the complement system are now known to participate in immunological injury when this system is activated in the skin, producing skin manifestations in the bullous dermatoses certain forms of vasculitis and erythema multiforme (Gigli, this volume). Skin lesions are also frequent in several profound immunodeficiency disorders that primarily involve the complement system (Day and Good, 1977). Acquired deficiencies of the complement system are manifested in many diseases, including systemic lupus erythematosus and lupus-like syndromes. Inherited isolated deficiencies of C1s, C1r, C2, C4, C5, or other complement components may also lead in some way to the development of lupus or lupus-like disease. Angioneurotic edema, and sometimes lupus as well, feature a deficiency of C1 esterase inhibitor. Patients with C1r deficiency suffer from infections which produce severe necrotizing skin lesions and destructive vasculitis, or sometimes lupus-like syndrome with similar skin rashes. C3 deficiency has also been linked with skin rash and skin infections, as well as severe pneumonia and susceptibility to pyogenic infections. C5 dysfunction is associated with Leiner's disease and susceptibility to gram-negative, bacterial, and yeast infections of skin and gut. C8 deficiency may occur in xeroderma pigmentosum, while C2 deficiency is complicated by a host of skin diseases including anaphylactoid purpura, dermatitis herpetiformis, several lupus-like illnesses, and fatal dermatomyositis. The skin lesions of pemphigus and bullous pemphigoid reflect the injurious influences of autoantibodies directed at particular components of the skin, as well as the capacity of these antibodies to reactivate complement components. Circulating immune complexes and complement system activation are regularly found in erythema multiforme, erythema multiforme bullosum, dermatitis herpetiformis, and severe bullous dermatitis of childhood. Several of these diseases are now known to be related to the $A_1$, $B_8$ haplotype or the $B_8$ antigen of the HLA supergene.

"Cold" abscesses of the skin, remarkable for their lack of inflammatory cells, have led to the characterization of Job's syndrome, in which a defective phagocytic response leaves the patient vulnerable to chronic pyogenic bacterial infections. Phagocyte dysfunction (Dahl *et al.*, this volume) has also been identified as one basis for several primary immunodeficiency diseases, all of which present with characteristic skin disorders. The granulomas of the skin and pyogenic dermatoses in patients with chronic granulomatous disease of childhood (Berendes *et al.*, 1957; Holmes *et al.*, 1966) are visible signs of an immunological dysfunction in which phagocytic cells fail to generate the oxidative burst leading to production of bactericidal $H_2HO_2$, singlet oxygen $O_2$, superoxide $O_2$ and OH-radical. The skin lesions of the Chediak-Higashi anomaly, of which oculocutaneous albinism and susceptibility to several forms of cancer are both regular features, are apparently caused by abnormal packaging of pigment (Baehner and Nathan, 1967; Boxer *et al.*, 1976). This abnormality is associated with poor chemotactic and

phagocytic function based at least in part on defects of the leukocytes' microtubule structure: a dramatic instance of how increased susceptibility to both infection and cancer is signaled by characteristic skin manifestations.

Both humoral and cell-mediated immunity functions are compromised in the Wiskott-Aldrich syndrome (Cooper *et al.*, 1968, Blaese *et al.*, 1974), which features hemorrhagic skin lesions, a peculiar form of eczema, and many skin infections. Ataxia telangiectasia is a disastrous illness which presents with a clinical tetrad including ataxia, cutaneous telangiectases, profound immunodeficiency, and susceptibility to many cancers (Boder, 1974). Extensive cutaneous moniliasis is the most common presenting symptom in infants with thymic aplasia (Rosen, 1976). An array of truly scourge-like dermatologic conditions may accompany all types of agammaglobulinemia: pyoderma with severe cicatrization of the skin, recurrent and severe furunculosis, eczema, verruca vulgaris, cutaneous granulomas, dermatomyositis-like syndrome with violaceous rash, and edema and induration of the subcutaneous tissues and even subcutaneous nodules (Good and Varco, 1955; Rosen, 1976). All this: and yet these miserable children cannot mount a wheal-and-flare reaction, so severe is their immunodeficiency.

As we continue to uncover the intricate mechanisms of the immune system, we can anticipate finding specific immune defects close to the source of other diseases which involve the skin. Immunologically-based therapy may then provide relief for illnesses which have defeated other forms of treatment. We have seen that the ancient affliction of leprosy may benefit from a form of immunologic engineering in which a transient T-cell reaction, stimulated by injections of allogeneic lymphocytes, generated enough cell-mediated immune activity for striking resolution of many of the patients' skin lesions (Lim *et al.*, 1974). Lymphokines, the immunological substances which appear to mediate many skin disorders, may also prove to be a highly potent therapeutic resource in the future, when basic science has achieved sufficient understanding of their mechanisms and the means to produce them in substantial quantities. We have learned that skin cancer, the most common neoplasm in the United States, is correlated with decreased immunity. The unusual immunopathology which accompanies head and neck carcinomas (Berlinger and Good, 1976) may yield more insights into the nature of this relationship. And it will surely be through immunological manipulation that we ultimately halt the courses of lupus erythematosus and scleroderma, pemphigus, erythema nodosum, and other autoimmune diseases.

While studies in these two disciplines have historically aided each other's purposes—the Gell and Coombs classification system, for example, has long demonstrated the importance of skin reactions as a medium for studying immunological injury—recent technical advances have associated the basic methods of immunology and dermatology more closely than ever before. Fluorescence microscopy, providing the means to observe and quantify the binding of immunoglobulins and complement to tissue, has been a major tool for studying the cutaneous and vascular immunopathology. Electron-microscopic studies have revealed striking histologic and inflammatory changes in bullous skin lesions. Our ability to detect histocompatibility antigens, besides enabling us to perform a variety of cell and organ transplantations, has helped us to define the gene-controlled aspects of several cutaneous disorders, including dermatitis herpetiformis, where the skin disease is inextricably linked to the alleles of the HLA supergene. Cyclic nucleotides are among the molecular factors of special interest to dermatologists, because they seem to be linked to the abnormal cell proliferation in psoriatic tissue, and could also underlie the immune dysfunctions in atopic dermatitis (Voorhees, this volume).