Current Perspectives in Immunodermatology

EDITED BY

Rona M. MacKie

Current Perspectives in Immunodermatology

EDITED BY
Rona M. MacKie
MD, FRCP, MRCPath, FRSE
Professor of Dermatology,
University of Glasgow, Glasgow, UK

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1984

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 1560 Broadway, New York,
N.Y. 10036, and by associated companies, branches and
representatives throughout the world.

First published 1984

ISBN 0 443 02668 8

British Library Cataloguing in Publication Data
Current perspectives in immunodermatology.—
(Current issues in clinical immunology and allergy)
1. Skin—Diseases
I. Mackie, Rona M. II. Series
616.5 RZ71

Library of Congress Cataloging in Publication Data
Current perspectives in immunodermatology.
(Contemporary issues in clinical immunology and
allergy)
Includes index.
1. Skin—Diseases—Immunological aspects—
Addresses, essays, lectures. I. Mackie, Rona. II. Series.
[DNIM: 1. Skin diseases—Immunology.
W1 C0769MQD/WR 140 C976]
RL72.C93 1983 661.5'079 83-20857

Printed in Great Britain by Butler & Tanner, Frome and London

Foreword

Dermatology, like other medical specialties, has benefited greatly from both the recent application of immunological techniques and the advances in understanding of immunological mechanisms of disease. Virtually all of the common dermatological disorders have demonstrable immunological lesions, although in many instances it is still unclear whether these findings are relevant primary processes or secondary to particular disease states. The series editors feel that the subject of immunodermatology should have high priority, since there is an urgent need to attempt to summarize the overwhelming amount of information which has accrued from investigations of the immunological basis of many skin disorders. We believe that the present volume has gone a long way in fulfilling this requirement. In each chapter, the authors are experts who can relate clinical manifestations to laboratory findings, review difficult and controversial areas, and, in most instances, reference carefully their views for those who wish to pursue certain areas in more depth. It is hoped that this volume will serve both to transmit new knowledge to practitioners and students and to update the specialist on recent advances in this field.

E. J. Goetzl
A. B. Kay

1984

Contributors

Thomas F. Anderson MD
Assistant Professor of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan, USA

R. StC. Barnetson MD, MRCP
Consultant Dermatologist, Royal Infirmary, Edinburgh; Formerly Clinical Research Physician, MRC Leprosy Project, Addis Ababa, Ethiopia

James M. Butler MB BS, FRACP, FACP
Fellow in Dermatology, Oregon Health Sciences University, Oregon, USA

Anthony C. Chu MB BS, MRCP
Senior Registrar, St John's Hospital for Diseases of the Skin, London, UK

J. J. Cream BSc, MD, FRCP
Consultant Dermatologist, Charing Cross Hospital, London, UK

Normand Dore
Instructor, Department of Dermatology, John Hopkins Medical Institute, Baltimore, Maryland, USA

Richard L. Edelson
Columbia Presbyterian Hospital, New York, USA

William L. Epstein MD
Professor and Chairman, Department of Dermatology, University of California, San Francisco, USA

Edward J. Goetzl MD
Director, Division of Allergy and Immunology, University of California, San Francisco, USA

Jon M. Hanifin MD
Associate Professor, Department of Dermatology, Oregon Health Sciences University, Oregon, USA

R. J. Hay DM, MRCP
Consultant Dermatologist, St Johns' Hospital for Diseases of the Skin, London, UK

Robert E. Jordan MD
Cutaneous Immunopathology Unit, Veterans Administration Medical Centre, Wood, Wisconsin, USA

Rona M. MacKie MD, FRCP, MRCPath, FRSE
Professor of Dermatology, University of Glasgow, Glasgow, UK

Herman Mogavero
Assistant Professor, Department of Dermatology, Johns Hopkins Medical Institute, Baltimore, Maryland, USA

John A. Parrish MD
Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, USA

Thomas T. Provost MD
Associate Professor and Chairman of Dermatology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

Eric O. Rasmussen BSc, MD
Resident in Dermatology, The Oregon Health Sciences University, Portland, Oregon, USA

J. H. Saurat
Clinique de Dermatololgie, Hôpital cantonal universitaire, Geneva, Switzerland

Nicholas Arthur Soter MD
Associate Professor of Dermatology, Harvard Medical School; Physician, Brigham and Women's Hospital, Boston, Massachusetts, USA

Robert S. Stern
Department of Dermatology, Harvard Medical School, Boston, Massachusetts, USA

John J. Voorhees MD
Professor and Chairman, Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Peter F. Weller AB, MD
Assistant Professor of Medicine, Harvard Medical School; Assistant Physician, Beth Israel Hospital, Boston, Massachusetts, USA

Bruce U. Wintroub
Department of Dermatology, University of California, San Francisco, USA

Kirk D. Wuepper MD
Professor of Dermatology, The Oregon Health Sciences University, Portland, Oregon, USA

Contents

Introduction

The availability of new immunological techniques has led in the past decade to an exciting and in some areas almost overwhelming number of publications in the field of dermatological immunology or immunodermatology. As new in vitro methods of assessing immunological abnormalities have become available, they have been applied to dermatological problems in attempt to understand aetiology, to aid diagnosis and in some cases as a form of therapy. Another area in which immunologists and dermatologists meet is in the management and investigation of the iatrogenic immunodermatosis, graft versus host disease. The early reports in the field of immunodermatology were mainly related to the bullous disorders and connective tissue or collagen diseases. In these areas immunological tests have now become well established aids to clinical diagnosis but newer immunological techniques have continued to be applied. In the case of pemphigus and bullous pemphigoid, immunochemical analysis should help us to identify accurately the antigenic components of the intercellular substance and basement membrane zone respectively, while in the connective tissue fields newer techniques have still further refined the identification of antinuclear components which under certain circumstances become antigenic. Correlation of these with distinct clinical presentations of disease may have valuable prognostic implications.

Common dermatoses which have recently been subjected to detailed immunological investigation include psoriasis, atopic dermatitis and drug reactions. In the case of psoriasis, there would appear to be two distinct schools of thought. One is that the observed immunological abnormalities are a primary cause, and the other is that they are a secondary consequence of the disease process. In atopic dermatitis there are clearly documented immunological abnormalities associated with the disease, but as yet no convincing unifying concept to explain the normal natural history of the condition. A large number of cutaneous adverse reactions to systemic drugs have an immunological basis, and in this case the problem is in unravelling the sequential roles played by different immunological mediators and also the development of a practical in vitro predictive model.

The resurgence of interest in ultraviolet light as therapy has resulted from the widespread introduction of photochemotherapy (PUVA) with systemic

psoralen and ultraviolet A (320–360 n.m. wavelength). This in turn has led to intensive investigation into the immunological abnormalities initiated by the application of all wavelengths of light on the skin, and the term 'photo-immunology' has been coined for this particular field of investigation.

All these and many other developments are included in this volume. The aim is to provide for the non dermatologist a useful and up-to-date review of current fruitful and collaborative investigation in the areas of dermatology in which immunological abnormalities are known or postulated to play a part. This is an extensive area of dermatology and because of this it is hoped that many practising dermatologists will also find it of value in updating their own knowledge of these particular areas. Each chapter is extensively referenced so that the reader may delve more deeply into the original work on the subject area reviewed.

The major immunobullous diseases

INTRODUCTION

The immunobullous skin diseases comprise most of the nonhereditary blistering diseases of man, and include the pemphigus group (pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, Brazilian pemphigus foliaceus, pemphigus erythematosus, and drug-induced pemphigus), the pemphigoid group (bullous pemphigoid, cicatricial pemphigoid, localized scarring pemphigoid and herpes gestationis), linear IgA bullous dermatosis, chronic bullous disease of childhood, epidermolysis bullosum acquisita, dermatitis herpetiformis and erythema multiforme. All of the above mentioned blistering skin diseases have specific immunopathologic features which allow us to better diagnose and classify them. A brief review of the important clinical, histopathologic and immunopathologic findings of the major bullous skin disease entities (the pemphigus and pemphigoid groups, dermatitis herpetiformis and erythema multiforme) is presented in this chapter. In addition, we have attempted to classify these diseases based upon their specific immunopathologic findings, including those based upon immunofluorescence (IF) and immunoelectron microscopy.

THE PEMPHIGUS GROUP

The pemphigus group of diseases, which have similar histopathologic and immunopathologic findings, are listed in Table 2.1. By far the most common and unfortunately the most severe form of the disease is pemphigus vulgaris, accounting for roughly 75% of all diagnosed cases of pemphigus[2]. Oral lesions, which are often the earliest presenting symptom in pemphigus vulgaris[2,43,68], are common and may precede skin lesions by four to five months. In rare

Table 2.1 The pemphigus group

Pemphigus vulgaris
Pemphigus vegetans
Pemphigus foliaceus
Fogo selvagem
Pemphigus erythematosus
Drug-induced pemphigus

instances, the disease may remain entirely confined to the oral cavity[68].Other mucous membranes, such as the nasal, vaginal, anal and laryngeal mucosa and the vermilion border of the lips are also often involved. Common sites of cutaneous involvement include the scalp, face, back, chest, and mucous membranes. When generalized, however, any area of the body may be involved.

Pemphigus vegetans represents a rare variant of pemphigus vulgaris. Although two types of this form of pemphigus have been recognized in the past, only the Neumann type of pemphigus vegetans is considered as a true member of the pemphigus group[43]. Early lesions of pemphigus vegetans are indistinguishable from pemphigus vulgaris. Later, lesions become hypertrophic and papillomatous, particularly in the intertriginous areas.

Histopathologically, lesions of both pemphigus vulgaris and pemphigus vegetans demonstrate suprabasalar intraepidermal blister formation and acantholysis. In pemphigus vulgaris, the cellular infiltrate may be sparse, although eosinophils, often in clusters (eosinophilic spongiosis) may be present in very early lesions[24]. In pemphigus vegetans, especially in verrucoid lesions, these infiltrates may be very heavy. Dissolution of the desmosomes is the earliest pathologic event observed by electron microscopy[32].

Less common than pemphigus vulgaris, pemphigus foliaceus is a less severe, superficial member of the pemphigus group[74]. Because of the superficial nature of the disease, blistering skin lesions are rarely seen; while shallow erosions with scaling and crusting are common. Oral lesions are extremely rare. Common areas of involvement include the scalp, face and chest. An interesting variant of pemphigus foliaceus is endemic to certain areas of South America. Called 'fogo selvagem' (wild fire), this disease entity is clinically, histopathologically and immunopathologically identical to true pemphigus foliaceus[11].

Pemphigus erythematosus is also a superficial member of the pemphigus disease group. First recognized by Senear and Usher[91], this condition combines clinical and serologic features of pemphigus and lupus erythematosus. Immunopathologically these patients usually have deposition of immunoglobulins and complement at the dermal-epidermal junction and antinuclear antibodies in their serum in addition to more typical findings of pemphigus[17]. Concurrent myasthenia gravis and thymoma has also been associated with this unique form of the disease[10,66].

Histopathologically, pemphigus foliaceus and pemphigus erythematosus are both characterized by intraepidermal bulla formation, but high in the epidermis, in or near the granular layer. A moderate infiltrate, mostly eosinophils is often present[74].

Drug-induced pemphigus was first reported by Degos et al[19], in a patient treated with D-penicillamine (β-β dimethyl cysteine) for hepatolenticular degeneration (Wilson's disease). Since that time, approximately 35 additional cases have thus far been documented[85,103]. Most of these patients manifest pemphigus foliaceus clinically. Several, however, have had either pemphigus vulgaris or pemphigus erythematosus[85]. In most instances, the eruption resolves spontaneously with cessation of D-penicillamine therapy.

Immunopathological findings

Pemphigus is an autoimmune disease which affects the skin. By indirect IF staining, autoantibodies reactive with an intercellular substance (ICS) of skin and mucosa are present in the serum of most patients with pemphigus[2,11]. These autoantibodies, which are of the IgG type, are found in all forms of pemphigus and represents an additional feature unifying the members of the pemphigus group. Levels of these antibodies fluctuate with activity of disease[72,83], and they react precisely at the sites of the primary pathologic process, the ICS area of skin. Recent evidence strongly suggests that these antibodies are responsible for the process of acantholysis.

By direct IF staining, both IgG and complement deposits have been noted in ICS areas of early acantholytic pemphigus lesions[33,50]. If performed properly, this test is positive in virtually all cases of pemphigus, including early pemphigus confined to the oral cavity[68]. Thus, pemphigus antibodies are capable of leaving the circulation and reacting 'in vivo' with autologous ICS antigen(s). In pemphigus vulgaris, these immune deposits are most intense in deep acantholytic areas (Fig. 2.1a), while in pemphigus foliaceus, the deposits are in the superficial layers of the skin (Fig. 2.1b).

As stated above, the ICS reactive autoantibody is the cause of loss of cohesion of epidermal cells (acantholysis). Using explants of skin in organ culture in the presence of pemphigus antibody, Schiltz et al[87,88] have shown that histopathologic changes similar to pemphigus and binding of autoantibody occurs in the explanted skin. These changes are apparent within 48 to 72 hours. Further studies have shown that this serum acantholytic activity resides in the IgG fraction and exerts its effect in the absence of complement. Further studies by this group[88] suggest that, when ICS reactive antibodies interact with antigen(s) on the epidermal cell surface, an enzyme(s) with proteolytic activity (pemphigus acantholytic factor) is released which causes acantholysis.

In similar studies but using both mouse and human epidermal cell tissue culture systems, Farb et al[25] and Singer et al[95] have shown that pemphigus antibodies result in loss of adhesion of epidermal cells. Serine proteinase inhibitors, such as alpha-2-macroglobulin and soybean trypsin inhibitor, would inhibit this process. These studies then also suggest that pemphigus antibodies react with an epidermal cell-surface antigen inducing enzyme release causing acantholysis.

Pemphigus has now been passively transferred in animals. Buschard et al[12] have developed a limited model in athymic nude mice with explanted oral mucosa. One week following explantation, pemphigus antibody was injected intraperitoneally. At sites of human oral mucosal explants, binding of antibody to ICS areas could be demonstrated and histologic changes of pemphigus occured. An even better animal model has recently been developed by Anhalt et al[5]. Using 24-hour-old mice, these investigators gave daily intraperitoneal injections of pemphigus serum. At about one week, blistering skin lesions developed which were histologically identical to pemphigus and which showed

antibody bound to the ICS areas. Thus, pemphigus has been successfully passively transferred to experimental animals.

Although past attempts to isolate and purify pemphigus antigen have been both disappointing and controversial, recent studies suggest that isolation and purification may now be feasible. Stanley et al[98], using an immunoprecipitation method and polyacrylamide SDS gel electropheresis, identified a 130,000 dalton protein which precipitated with five of seven pemphigus sera. Geoghegan et al[29], using direct tissue isoelectric focusing and Western Blots on nitrocellulose showed binding of pemphigus IgG to 2 to 3 protein bands migrating in the basic region of the gels. These new approaches may shed new light on the nature of the antigen(s) reactive with pemphigus antibodies.

Although initial studies failed to show that ICS reactive antibodies activate complement, recent investigators from Japan have been successful[33]. By in vitro complement staining some of these antibodies have been shown to fix complement, particularly those found early in the disease process. Several years ago, Sams et al[84] showed that pemphigus antibody activity resides in subclasses of IgG that fix complement. The abilities of pemphigus antibodies to activate complement, however, remains controversial, and until newer methods are employed this controversy will continue.

A variety of other immunologic perturbations suggestive of involvement of the complement system and immune complex formation have also been reported in pemphigus. These findings include low total hemolytic complement and individual complement components in pemphigus blister fluids[45],

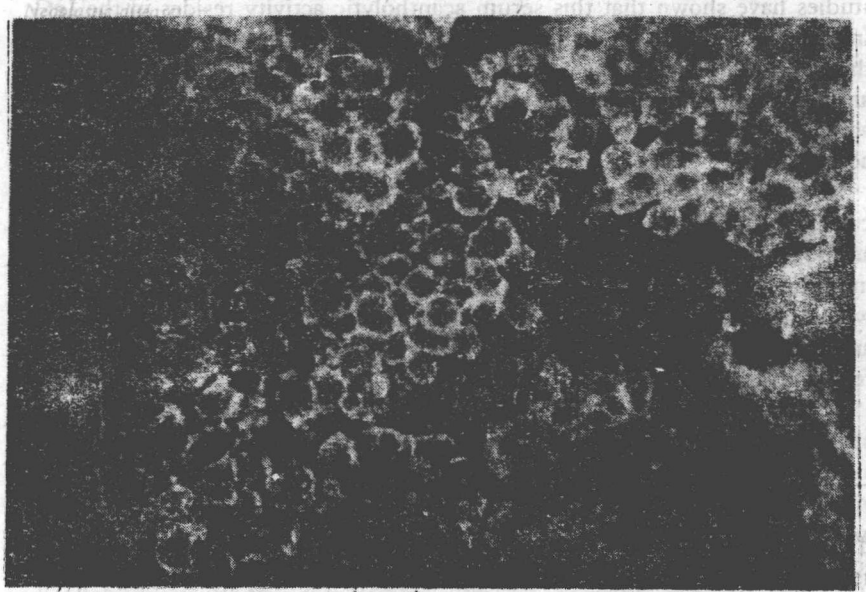

Fig. 2.1a Direct immunofluorescence (IF) studies of patients with pemphigus using labeled antiserum to IgG. a. Pemphigus vulgaris X400

high molecular weight serum and blister fluid anticomplementary activity[48], elevated serum Clq binding activity[100], and serum cryoproteins which contain IgG with pemphigus antibody activity and various complement components[70]. Whether complement activation and immune complex formation play any role in the pathogenesis of pemphigus or are epiphenominal, however, remains to be determined.

THE PEMPHIGOID GROUP

The pemphigoid group (Table 2.2) includes bullous pemphigoid, herpes gestationis, cicatricial pemphigoid and localized scarring pemphigoid (Brunsting-Perry). Despite different clinical presentations, this group has similar histopathologic and immunopathologic findings and is characterized by immunoglobulin and complement deposition to the lamina lucida region of the basement membrane zone (BMZ).

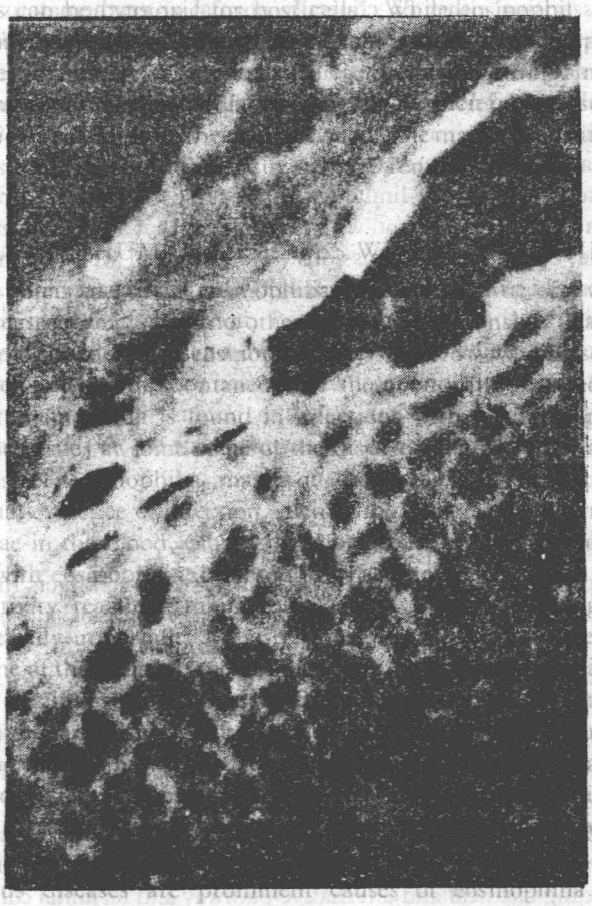

Fig. 2.1b Pemphigus foliaceus X400

Table 2.2 The pemphigoid group

Bullous pemphigoid
Herpes gestationis
Cicatricial pemphigoid
Localized scarring pemphigoid

Bullous pemphigoid

For many years, bullous pemphigoid had been confused with other blistering skin diseases such as pemphigus, dermatitis herpetiformis and erythema multiforme. First recognized as a separate, distinct clinical entity by Lever[64] the term bullous pemphigoid was chosen because of the close clinical similarity to pemphigus vulgaris, but with the histopathological absence of acantholysis.

Clinically, the major feature of bullous pemphigoid is the presence of large tense blisters arising either on clinically normal or erythematous skin. The flexor surfaces of the forearms, the groin, the axillae and lower abdomen are common sites of involvement. Lesions usually show a good tendency to heal and only rarely extend peripherally. Lesions in the mucous membranes are less common than in pemphigus vulgaris, are rarely the initial manifestation, and usually appear as intact blisters.

The disease is usually self-limited with a course characterized by periodic remissions and exacerbations and with recurrences that are less severe than the initial episode. Spontaneous remissions have also been well-documented[65].

Bullous pemphigoid occurs predominantly in the sixth, seventh and eighth decades of life[65,96], but well-documented cases have also been reported in children[9]. Age matched studies reported by Stone & Schroeter[99] have failed to substantiate the previous notion of an increased incidence of malignancy. The mortality rate is thought to be low, although, because of the age of many of the patients, death from unrelated causes may intervene before the disease has run its course.

Immunopathology

Bullous pemphigoid is also an autoimmune disease which affects the skin. By indirect IF staining, autoantibodies reactive with the BMZ of skin and mucosa are present in serum in about 75% of patients with this disease[11,44]. These antibodies are of the IgG type and are found in all subclasses of IgG[84]. They will avidly fix a variety of complement components[42,63].

By direct IF staining, IgG may be detected bound in vivo to the BMZ of skin lesions[53]. Other immunoglobulins, including IgM, IgA, IgD and IgE have also been detected[18,53,79], but much less frequently. Deposition of C3 occurs in virtually all bullous pemphigoid skin lesions (Fig. 2.2) and at times in the absence of immunoglobulins[3,18,53,79]. Other components of the complement system, including classical and alternative pathway and terminal components, are also present bound to the BMZ of perilesional skin[49,79]. By immunoelectron

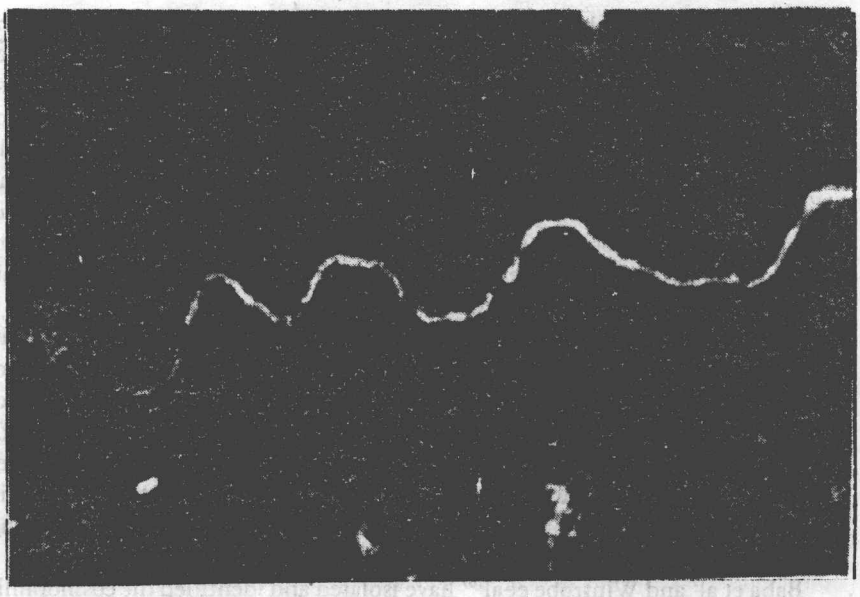

Fig. 2.2 Direct IF staining of perilesional skin from a patient with bullous pemphigoid demonstrating C3 deposition to the basement membrane zone (BMZ) X250

microscopy employing horseradish peroxidase methods, these immunoreactants have been localized to the lamina lucida region of the BMZ[36,89].

Several attempts have been made to isolate and purify antigens reactive with bullous pemphigoid antibodies. It has now been clearly demonstrated that this antigen(s) is produced by basal cells and deposited in the BMZ[21,108]. Using normal human skin, Diaz et al[20] isolated a protein with a molecular weight of 20 000 which blocked IF reactivity of BMZ antibodies. In another study these same investigators isolated a similar antigen from human urine[22]. This latter study, however, suggested that BMZ antigen was forming 35 000 to 74 000 molecular weight polymers. Stanley et al[97], using radiolabeled amino acids and immunoprecipitation, isolated an antigen with a molecular weight of 200 000, more than ten times the size of the antigen originally isolated by Diaz et al[20], a situation which has generated controversy. Further, Zhu & Bystryn[110] have demonstrated different reactivities for bullous pemphigoid antibodies using indirect IF and multiple substrates. Thus, the true nature of bullous pemphigoid antigen(s) needs further elucidation.

Initial attempts at passively transferring bullous pemphigoid with serum were discouraging[82]. Anhalt et al[4] have recently passively transferred the disease by injecting bullous pemphigoid IgG into rabbit corneas. Binding of antibody and complement to the BMZ was demonstrated, and by routine histopathology, neutrophils were seen clustered along the BMZ. No experimental animal model, however, has thus far been developed.