CONTINUING MEDICAL EDUCATION

The new pemphigus variants

Neha D. Robinson, MD,[a] Takashi Hashimoto, MD,[b] Masayuki Amagai, MD,[c] and
Lawrence S. Chan, MD[a,d] *Chicago, Illinois, and Kurume and Tokyo, Japan*

Pemphigus describes a group of autoimmune diseases characterized by blisters and erosions of the skin and mucous membranes, acantholysis by histology, and autoantibodies directed against epidermal cell surface components. Since the early 1970s, the following new clinical variants of pemphigus have been reported: pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus. In recent years, significant data have been obtained from laboratory investigation on these rare and atypical variants, especially regarding their specific target antigens. We review these variants, their clinical presentations, histologic findings, immunopathology, target antigens, theories of pathogenesis, treatment modalities, and clinical courses. (J Am Acad Dermatol 1999;40:649-71.)

Learning objective: After completing this article, readers should be familiar with pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus. On the basis of their unique clinical, histologic, and immunofluorescence findings, readers should also be able to differentiate these new pemphigus variants from the common forms of pemphigus.

Pemphigus describes a group of chronic bullous diseases, originally named by Wichmann in 1791.[1] All acquired forms of pemphigus are now characterized as autoimmune blistering diseases presenting clinically with flaccid intraepidermal blisters and erosions of the skin and mucous membranes, histologically with acantholysis, and immunopathologically with in vivo–bound and circulating autoantibodies against keratinocyte

Copyright © 1999 by the American Academy of Dermatology, Inc.

0190-9622/99/$8.00 + 0   **16/2/96936**

cell surface components.[2] Pemphigus is usually divided into two distinct categories depending on blister location: pemphigus vulgaris and pemphigus foliaceus, each with its own variants (pemphigus vegetans and pemphigus erythematosus, respectively). Evidence has revealed that the IgG autoantibodies of patients with pemphigus vulgaris and pemphigus foliaceus recognize desmosomal components, desmoglein 3 and desmoglein 1, respectively.[3-5] A complete review of these diseases, including pemphigus vulgaris, foliaceus, vegetans, and erythematosus, has been previously published.[2] During the past 3 decades, rare forms of pemphigus have been described, including pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus. Most of the autoantigens targeted by the autoantibodies from patients affected by these new pemphigus variants have been recently identified. In light of this new information, this article extensively reviews the clinical presentation, histology, immunopatholo-

Table I. Clinical presentation, histology, and immunofluorescence findings of the new pemphigus variants

Disease	Clinical presentation	Histopathology	DIF	IIF
Pemphigus herpetiformis	Pruritic, erythematous, vesicular, bullous, or papular lesions, often in herpetiform pattern; occasional mucous membrane involvement	Eosinophilic spongiosis, w/ or w/o acantholysis; intraepidermal pustules filled w/ eosinophils or neutrophils	IgG deposits in upper or entire epidermal cell surfaces	Circulating IgG autoantibodies to epithelial cell surfaces
IgA pemphigus	Pruritic, flaccid vesicles and/or pustules in annular pattern with central crusting, sometimes hypopyon; rare mucous membrane involvement	IEN type: Suprabasal pustules, neutrophil infiltration, scanty acantholysis SPD type: Subcorneal pustules, neutrophil infiltration, scanty acantholysis	IEN type: IgA deposits in lower or entire epidermal cell surfaces SPD type: IgA deposits in upper epidermal cell surfaces	Circulating IgA autoantibodies to epithelial cell surfaces (in 50% of cases)
Paraneoplastic pemphigus	Polymorphous skin eruption, consisting of blisters, erosions, and targetoid lesions; severe mucous membrane involvement	Suprabasilar intraepithelial acantholysis, Keratinocyte necrosis, and vacuolar-interface change	IgG deposits in entire epidermal cell surfaces +/– granular-linear complement deposition along basement membrane zone and epidermal cell surfaces	Circulating IgG autoantibodies to epithelial cell surfaces; circulating IgG autoantibodies to rat bladder epithelium in 75% of cases (sensitivity)

+/–, With or without; *DIF,* direct immunofluorescence; *IIF,* indirect immunofluorescence; *w/,* with; *w/o,* without.

gy, target antigens, and treatment of these new forms of rare and atypical pemphigus.

EPIDEMIOLOGY AND CLINICAL PRESENTATION (Table I)
Pemphigus herpetiformis

Pemphigus herpetiformis is recognized as a distinct variant of pemphigus by its pruritus, the invariable presence of eosinophils and/or neutrophils, and its tendency to respond to sulfones. The disease was originally named and the diagnostic criteria were described by Jablonska et al[6] in 1975, although patients with similar clinical phenotypes were described as early as 1955 by Floden and Gentale[7] under the heading "dermatitis herpetiformis with acantholysis." Since then at least 40 additional cases have been presented in the literature.[8-18] The study by Maciejowska, Jablonska, and Chorzelski[8] found 15 cases of pemphigus herpetiformis out of 205 cases of pemphigus (7.3%). In 1998, Micali, Musumeci, and Nasca[19] performed an epidemiologic analysis of 84 cases of pemphigus in eastern Sicily and found

5 cases of pemphigus herpetiformis (6%). In this study, the mean age at onset was 65 years (range, 45-83 years of age). In other studies, the age range at onset was 31 to 81 years without a male or female predilection.[8,9,20]

Pemphigus herpetiformis combines the clinical features of dermatitis herpetiformis with the immunologic and histologic features of pemphigus (Fig 1). In the study of 15 patients by Maciejowska, Jablonska, and Chorzelski,[8] all patients presented with erythematous, vesicular, bullous, or papular lesions, often in a herpetiform pattern. Oral mucous membranes were involved in 4 cases, and severe pruritus accompanied the eruption in 6 patients. In cases of other studies, the skin was the only affected site.[19] Most patients described by Santi et al[9] experienced pruritus and an eruption characterized by superficial vesicles and inflammatory plaques. Unfortunately, the clinical presentation of pemphigus herpetiformis is atypical, and the lesions are often initially recognized as various other bullous diseases, such as dermatitis herpetiformis, bullous pemphigoid, linear IgA bullous

Table II. Differential diagnoses of the new pemphigus variants

Pemphigus variants	Differential diagnoses
Pemphigus herpetiformis	1. Dermatitis herpetiformis 2. Pemphigus foliaceus 3. Bullous pemphigoid 4. Linear IgA bullous dermatosis 5. Pemphigus vulgaris
IgA pemphigus	1. Subcorneal pustular dermatosis 2. Dermatitis herpetiformis 3. Pemphigus foliaceus 4. Pemphigus herpetiformis 5. Linear IgA bullous dermatosis
Paraneoplastic pemphigus	1. Erythema multiforme major 2. Erythema multiforme with pemphigus vulgaris 3. Toxic epidermal necrolysis 4. Epidermolysis bullosa acquisita 5. Pemphigus vulgaris 6. Drug-induced pemphigus 7. Bullous pemphigoid 8. Cicatricial pemphigoid 9. Aphthous stomatitis 10. Behçet's disease 11. Lichen planus with pemphigus vulgaris 12. Persistent herpes simplex virus infection

Fig 1. Clinical presentation of pemphigus herpetiformis. Annular, erythematous plaques with peripheral vesicles.

Fig 2. Clinical presentation of the SPD type of IgA pemphigus. Cluster of vesicles with central crusting on erythematous skin.

dermatosis, or pemphigus foliaceus[8] (Table II). Nevertheless, severe pruritus seems to be a commonly presented symptom.[9,11]

IgA pemphigus

IgA pemphigus is a newly characterized group of autoimmune intraepidermal blistering diseases presenting with a vesiculopustular eruption, neutrophil infiltration, acantholysis, and in vivo–bound and circulating IgA autoantibodies that target cell surface components of the epidermis. IgA pemphigus as a disease entity was first described by Wallach, Foldes, and Cottenot[21] in 1982 under the name *subcorneal pustular dermatosis and monoclonal IgA,* although IgA deposition in the epidermis in patients with the clinical phenotype of subcorneal pustular dermatosis was reported in 1979 by Sneddon and Wilkinson and others.[22,23] Subsequently, multiple cases have been reported under several different names, including *intraepidermal neutrophilic IgA dermatosis, intercellular IgA dermatosis, IgA pemphi-*

gus foliaceus, IgA herpetiform pemphigus, intraepidermal IgA pustulosis, and *intercellular IgA vesiculopustular dermatosis.*[21,24-30]

There are two distinct types of IgA pemphigus: the subcorneal pustular dermatosis (SPD) type and the intraepidermal neutrophilic (IEN) type, also referred to as "IgA pemphigus foliaceus" and "IgA pemphigus vulgaris," respectively.[24,31] However, a consensus has not been reached regarding this nomenclature. Patients with both types of IgA pemphigus clinically present with flaccid vesicles or pustules or both on erythematous or normal skin (Figs 2 and 3). The pustules tend to coalesce to form an annular or circinate pattern with crusts in the central area. The sites of predilection are the axillary and groin areas, but the trunk, proximal extremities, and lower aspect of the abdomen are

Fig 3. Clinical presentation of the IEN type of IgA pemphigus. Pustules with central crusting on erythematous skin.

commonly involved. Mucous membrane involvement is rare.[22,24,32] Pruritus is also a significant symptom that may interfere with the patient's daily activities. An unusual presentation of a widespread vesicular eruption with herpetiform distribution, similar to pemphigus herpetiformis, was described in a patient with the SPD type of IgA pemphigus as well.[33]

In the literature to date, there are more than 60 cases of IgA pemphigus, with a slight predominance of the SPD type. IgA pemphigus usually occurs in middle-aged or elderly persons, although occasional reports of the disease in childhood have been described. The disease has an average age at onset of approximately 48 years (range, 5-92 years). There is also a slight female predominance (56%).[22,30-32,34-36] There seems to be no particular geographic distribution; patients have been described throughout Japan, Europe, and the United States. A pemphigus vegetans variant of the IEN type of IgA pemphigus occurring during immunosuppressive drug therapy was described in a 7-year-old boy.[36] Another report described a 7-year-old girl with lesions involving not only the skin, but also the oral mucosa.[37]

Paraneoplastic pemphigus

Before the formal characterization by Anhalt et al[38] in 1990 as an autoimmune disease with a polymorphous blistering eruption, mucocutaneous ulcerations, and an underlying neoplasm, several cases of paraneoplastic pemphigus were described in the literature, often reported as unusual cases of pemphigus vulgaris, erythema multiforme, or an unusual paraneoplastic bullous disease.[39] The 5 diagnostic criteria initially proposed for paraneoplastic pemphigus include the following[38]:

1. Painful mucosal ulcerations and blisters and a polymorphous skin eruption, with papular lesions progressing to blisters and erosive lesions affecting the trunk, extremities, palms, and soles, in the context of an occult or confirmed underlying neoplasm

2. Histologic findings of vacuolar interface change, keratinocyte necrosis, and intraepidermal acantholysis

3. Deposition of IgG and C3 in the epidermal intercellular spaces, and granular-linear complement deposition along the epidermal basement membrane zone on direct immunofluorescence

4. Serum autoantibodies that bind not only to the cell surfaces of skin and mucosa in a pattern typical of pemphigus, but also to simple, columnar, and transitional epithelia

5. Serum autoantibodies that recognize epidermal antigens of 250, 230, 210, and 190 kd by immunochemical techniques such as immunoprecipitation

A new term, *neoplasia-induced pemphigus,* as well as a modification of the original set of diagnostic criteria was later proposed by Camisa and Helm[40] in 1993. This term was proposed after an observation that the mucocutaneous changes may persist after the tumor was in complete remission.[40] However, for the remainder of this review article, we will use the term *paraneoplastic pemphigus* until a general consensus has been reached. The modified criteria proposed by Camisa and Helm are as follows[40]:

Major criteria:
    Polymorphous mucocutaneous eruption
    Concurrent internal neoplasia
    Characteristic serum immunoprecipitation findings
Minor criteria:
    Positive cytoplasmic staining of rat bladder epithelium by indirect immunofluorescence
    Intercellular and basement membrane zone immunoreactants on direct immunofluorescence of perilesional tissue
    Acantholysis in biopsy specimen from at least one anatomic site of involvement

According to the proposal by Camisa and Helm,[40] patients should be considered to have neoplasia-induced pemphigus if all 3 major or 2 major and 2 or more minor criteria are met.

The cutaneous lesions of paraneoplastic pemphigus are quite variable, consisting of a mixture of blisters, erosions, and target lesions (Fig 4). In the initial study by Anhalt et al,[38] patients experienced pruritic blisters that ruptured easily, affecting the upper half of the trunk, head and neck, and proximal extremities. Occasionally, lesions on the extremities consisted of tense blisters or target lesions with central blister formation, resembling those seen in bullous pemphigoid or erythema multiforme.[38,41-43] Confluent erythema in the V area of the upper chest and back was also common.[38] It has been observed that some eruptions resembling lichen planus or lichen planus pemphigoides occur as well. These lichenoid eruptions may be the sole cutaneous manifestations of the disease, or they may develop in lesions that had previous blistering.[44-47] The occurrence of blisters and lichenoid lesions on the palms and soles can often be used to differentiate paraneoplastic pemphigus from pemphigus vulgaris, in which lesions of the palms and soles are unusual. Patients with chronic lichenoid skin lesions may occasionally also have ulcerative paronychial lesions, which can be painful and debilitating.[39]

The most observed clinical feature of paraneoplastic pemphigus is an intractable stomatitis, which is usually the earliest presenting sign, and is extremely resistant to therapy.[39] The stomatitis consists of painful erosions and ulcerations of the oropharynx and vermilion borders of the lips.[38,39] Most patients also have a severe pseudomembranous conjunctivitis.[38] Lam et al[48] describe a patient who initially had an erosive conjunctivitis, which progressed to scarring and bilateral obliteration of the conjunctival fornices. Labial, gingival, buccal, lingual, esophageal, laryngeal, tracheobronchial, nasopharyngeal, oropharyngeal, vaginal, and penile mucosal lesions have also been observed.[38,43,48,49] Fullerton et al[43] describe a patient with dyspnea out of proportion to findings by arterial blood gas analysis and chest radiography. Bronchoscopy revealed a denuded respiratory epithelium, and direct immunofluorescence of a biopsy specimen of the bronchial mucosa was consistent with paraneoplastic pemphigus. Postmortem examination revealed pemphigus-like lesions of the esophageal and tracheal mucosa.[43] Involvement of the gastrointestinal and respiratory epithelia was also suggested by Lam et al[48] by bronchoscopy and upper gastrointestinal radiologic studies, but the pathology from either site was not documented. Only 1 case has been
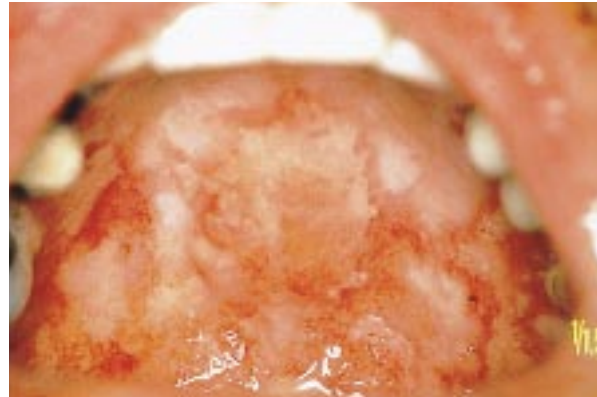

Fig 4. Clinical presentation of paraneoplastic pemphigus. Erosions and ulcerations of the palate.

described with the total absence of mucosal involvement, and this patient had a favorable outcome with corticosteroid treatment alone.[50]

As stated in the diagnostic criteria, paraneoplastic pemphigus is associated with an underlying neoplasm, either malignant or benign. In approximately two thirds of cases, the skin disease occurs in patients with an existing neoplasm. In the remaining one third of cases, neoplastic lesions are detected after the mucocutaneous disease occurs.[39] Thus examination for an occult neoplasm is important in suspected cases of paraneoplastic pemphigus, especially with computed tomographic scanning of the chest, abdomen, and pelvis.[39]

The various neoplasms associated with paraneoplastic pemphigus in decreasing order of frequency are as follows: non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's tumor, thymoma (malignant and benign), poorly differentiated sarcoma, Waldenström's macroglobulinemia, inflammatory fibrosarcoma, bronchogenic squamous cell carcinoma, round-cell liposarcoma, Hodgkin's disease, and T-cell lymphoma.[38,40,43,44,46,47,50-63] One patient has been described by Fullerton et al[43] in whom paraneoplastic pemphigus developed while his non-Hodgkin's lymphoma was in apparent complete remission after autologous bone marrow transplantation. Autopsy revealed good engraftment of the autologous bone marrow, without gross or microscopic evidence of recurrent lymphoma.[43] Another case report describes a patient with paraneoplastic pemphigus in the absence of a known neoplasm. Unfortunately, an autopsy was not performed.[41]
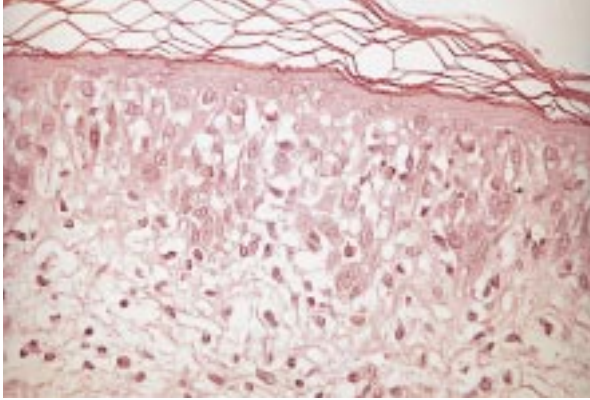
Fig 5. Histologic findings in pemphigus herpetiformis. Early acantholysis with a mixed inflammatory cell infiltrate in the epidermis. (Hematoxylin-eosin stain; original magnification ×100.)
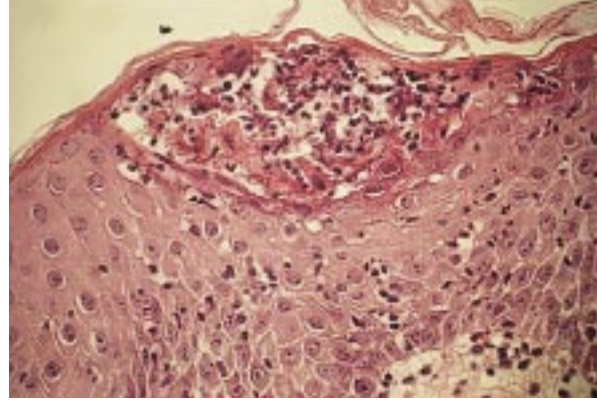

Fig 6. Histologic findings in the SPD type of IgA pemphigus. Subcorneal blister with neutrophil infiltration. (Hematoxylin-eosin stain; original magnification ×100.)

What is significant in this list of neoplasms is that Castleman's tumor is disproportionately associated with paraneoplastic pemphigus.[39] Castleman's tumor is also referred to as angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, and Castleman's pseudolymphoma.[39] Affected nodes appear predominantly in the thorax and abdominal and pelvic retroperitoneal spaces; extranodal forms of the disease also occur.[39] Castleman's tumors have also been associated with other autoimmune disorders, such as myasthenia gravis and autoimmune cytopenias.[64-66]

Since the original description of paraneoplastic pemphigus by Anhalt et al[38] in 1990, more than 70 cases of paraneoplastic pemphigus have been described in the literature to date.[39-44,46-48,50-63,67] There is a wide geographic distribution, including the following ethnicities: Polish, Japanese, Dutch, Iranian, Hispanic, Bosnian, and American.[38,46,53,54,58] Age at onset ranges from 7 to 77 years (mean, 51 years).* Paraneoplastic pemphigus is rare in children, although two case reports have described paraneoplastic pemphigus in children 7 and 13 years of age.[53,58] There does not seem to be a gender predominance.[40]

HISTOPATHOLOGY
Pemphigus herpetiformis

The histologic findings in pemphigus herpetiformis vary greatly and often are noncontributory. In the studies by Jablonska et al[6] and Maciejowska,

---

*References 38-44, 46-48, 50-53, 55, 56, 58, 59, 61-63, 67.

Jablonska, and Chorzelski,[8] biopsy specimens revealed various features: eosinophilic spongiosis, with or without isolated acantholytic cells in the upper layers of the epidermis; abortive bullae with slight acantholysis; or intraepidermal pustules filled with neutrophils and eosinophils. On the contrary, biopsy specimens in the study by Santi et al[9] invariably revealed eosinophilic spongiosis and acantholysis. Recent reports have indicated a wide variation of inflammatory cell infiltration with approximately 20% eosinophil-dominant, 20% neutrophil-dominant, and 60% mixed neutrophils and eosinophils.[10] Because the histologic findings vary according to the evolution of the skin lesions and typical findings of pemphigus emerge only later in the disease process, several biopsies may be needed to reach the correct diagnosis (Fig 5).

IgA pemphigus

Histopathologic examination of the two IgA pemphigus types documents the level of intraepidermal pustule or blister formation. In the SPD type of IgA pemphigus, pustules are located subcorneally in the upper epidermis (Fig 6), whereas in the IEN type, suprabasilar pustules in the lower or entire epidermis are present (Fig 7). There is an accompanying superficial acantholysis that is frequently sparse, as well as a significant neutrophil infiltration.[22,24,31]

Paraneoplastic pemphigus

The histologic findings of lesions in paraneoplastic pemphigus show considerable variability,
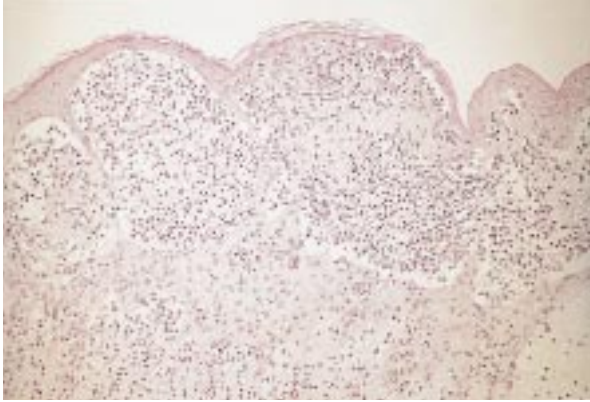
Fig 7. Histologic findings in the IEN type of IgA pemphigus. Intraepidermal blister with acantholysis and a predominantly neutrophil infiltration. (Hematoxylin-eosin stain; original magnification ×50.)
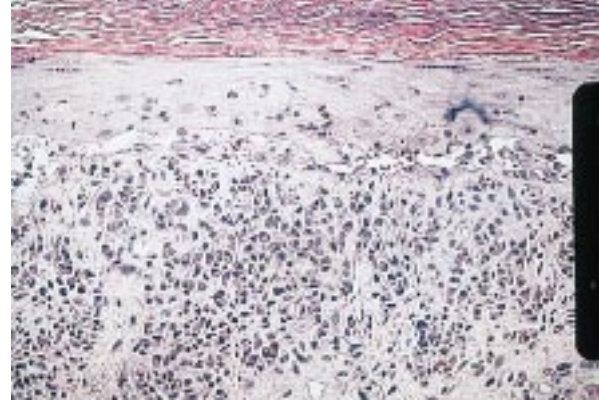

Fig 8. Histologic findings of paraneoplastic pemphigus. Suprabasilar acantholysis and cleft formation, dyskeratotic keratinocytes, and an infiltration of mononuclear cells in a lichenoid pattern. (Hematoxylin-eosin stain; original magnification ×75.)

reflecting the polymorphism of the clinical lesions.[38,39,67] The stomatitis is severe, and many biopsy specimens from ulcerative lesions will only demonstrate nonspecific inflammation.[39] Anhalt et al[38] describe suprabasilar intraepithelial acantholysis, necrosis of individual keratinocytes, and vacuolar-interface change as the predominant histologic findings in their series of patients (Fig 8). According to Horn and Anhalt,[67] the major histologic features include epidermal acantholysis, suprabasilar cleft formation, dyskeratotic keratinocytes, vacuolar change of the basilar epidermis, and epidermal exocytosis of inflammatory cells. These diagnostic features are expressed in clinical lesions demonstrating vesiculation. The perivascular inflammatory cell infiltrate was mainly composed of mononuclear cells, probably lymphocytes.[67] A unique combination of suprabasal acantholysis and dyskeratotic keratinocytes was visualized throughout the epidermis in 44% of specimens. A "tombstone appearance" of the basal keratinocytes lining the floor of the blister of suprabasal clefts was also noted in some cases. Unlike many eruptions with interface changes, no dyskeratotic cells were noted in the upper dermis. There was no evidence of cellular atypia or vasculitis present in any of the 16 specimens.[67]

The suprabasilar acantholysis and blister formation of paraneoplastic pemphigus are similarly seen in pemphigus vulgaris, but the characteristic pemphigus vulgaris findings of neutrophils and eosinophils in the papillary dermis and eosinophilic

epidermal spongiosis are not seen in paraneoplastic pemphigus.[67] The suprabasal cleft does not progress with overt formation of bullae, distinguishing paraneoplastic pemphigus histologically from herpes gestationis and incontinentia pigmenti, which are characterized by both bullae and dyskeratotic keratinocytes.[67] The lichenoid skin lesions demonstrate areas of dense lymphocytic infiltrate in the papillary dermis and individual lymphocytes infiltrating in the epithelium with occasional individual cell necrosis.[39] Specimens that display the features of interface dermatitis (dyskeratotic keratinocytes, basal vacuolization, and epidermal exocytosis) cannot always be distinguished histologically from other disorders with interface dermatitis, including erythema multiforme, toxic epidermal necrolysis, fixed drug eruption, lupus erythematosus, graft-versus-host disease, and secondary syphilis. The patterns of inflammation, absence of acantholysis, and immunofluorescence findings, however, distinguish these diseases from paraneoplastic pemphigus.[67]

IMMUNOPATHOLOGY
Pemphigus herpetiformis

Because the clinical presentation and histologic findings are often atypical, the more reliable basis for diagnosis of pemphigus herpetiformis is immunopathology. Direct immunofluorescence performed on perilesional skin biopsy specimens has invariably revealed in vivo–bound IgG deposition at the keratinocyte cell surface primarily in the
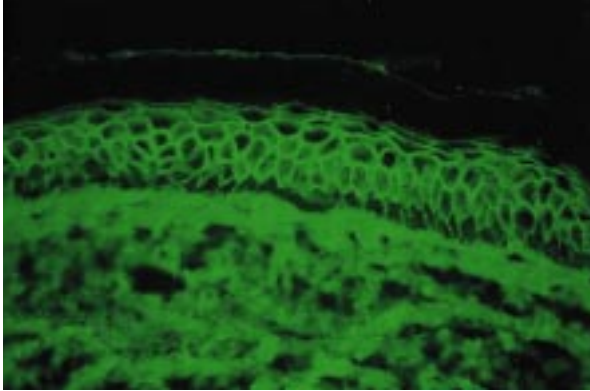
Fig 9. Immunofluorescence findings of pemphigus herpetiformis. Direct immunofluorescence demonstrates IgG deposition at the epidermal cell surfaces, sparing the basal layers. (Original magnification ×100.)
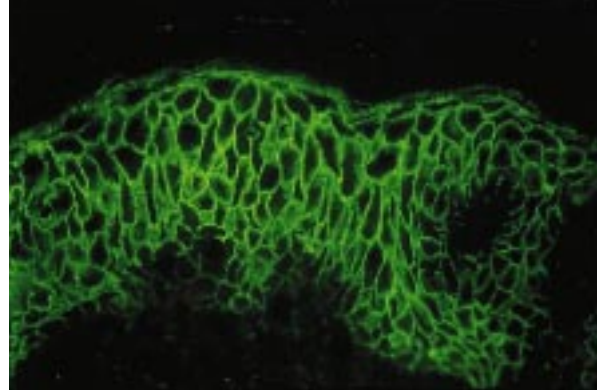

Fig 11. Immunofluorescence findings of the IEN type of IgA pemphigus. Indirect immunofluorescence demonstrates circulating IgA autoantibodies binding to the cell surfaces of the entire epidermis of normal human skin. (Original magnification ×100.)
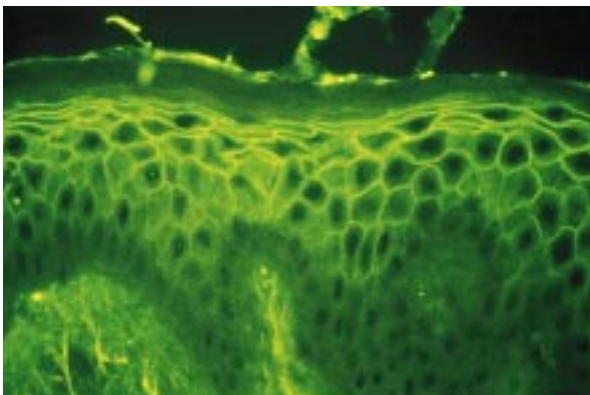

Fig 10. Immunofluorescence findings of the SPD type of IgA pemphigus. Indirect immunofluorescence demonstrates circulating IgA autoantibodies binding to the upper epidermal cell surfaces of normal human skin. (Original magnification ×100.)

upper epidermis (Fig 9).[6,8,9,11] Indirect immunofluorescence has also demonstrated circulating IgG anti-epithelial cell surface autoantibodies in most pemphigus herpetiformis patients described.[6,8,9,11] The IgG4 subclass was found to be the predominant IgG subclass of in vivo–bound and circulating autoantibodies in the studies by Santi et al,[9] Kubo et al,[20] and O'Toole et al.[68]

IgA pemphigus

IgA deposition in the intercellular substance of the epidermis is present in all cases of IgA pemphigus by direct immunofluorescence of perile-

sional skin specimens, usually in a pattern similar to pemphigus IgG deposition.[22,24-27,32,34] In the SPD type of IgA pemphigus, IgA deposition is limited to the upper epidermal cell surfaces (Fig 10), whereas in the IEN type of IgA pemphigus, there is intercellular IgA deposition restricted to the lower epidermis or throughout the entire epidermis (Fig 11).[24,30,32] The subclass of in vivo–bound and circulating IgA autoantibodies has also been determined and is exclusively IgA1.[22,26,31,37]

Despite the consistent in vivo deposition of IgA in patients' skin, only approximately 50% of patients have detectable circulating autoantibodies by indirect immunofluorescence.[22,24,28] In the study by Hashimoto, Ebihara, and Nishikawa[32] in 1996, nearly all patients' sera (16 of 17) demonstrated circulating autoantibodies using indirect immunofluorescence on normal human skin. Low serum titers were also noted in the majority of these cases, usually between 1:10 and 1:320.[22,24,31,32]

The study by Supapannachart and Mutasim[69] in 1993 also demonstrated that a patient's serum specimen that did not exhibit circulating IgA autoantibodies by standard indirect immunofluorescence techniques on standard substrates, such as monkey esophagus or normal human skin, did contain antibodies on prolonged incubation under explant culture conditions. This study proposed that skin explant culture may be more sensitive in detecting circulating autoantibodies, and this tech-

nique may be utilized in detecting IgA pemphigus antibodies in serum specimens that are negative by standard indirect immunofluorescence.

Paraneoplastic pemphigus

Direct immunofluorescence of lesional or peri-lesional skin or mucosa specimens has invariably revealed IgG deposition in the epidermal cell surfaces, in a pattern typical to that seen in pemphigus vulgaris, but often in a focal or faint deposition pattern (Fig 12).[38,39,67] A distinctive finding was the combined presence of a granular-linear complement deposition pattern along the basement membrane zone as well as the epidermal cell surfaces.[38] False-negative direct immunofluorescence results are more common in paraneoplastic pemphigus than in pemphigus vulgaris; therefore repeated biopsies may be necessary to establish the diagnosis.[39]

The diagnosis of paraneoplastic pemphigus can also be established by the presence of circulating IgG autoantibodies by indirect immunofluorescence examination of monkey esophagus, human skin, and mouse skin. Titers usually range from 1:320 to 1:5120. The autoantibodies have been found to be polyclonal, with IgG subclasses in the following descending order: IgG1, IgG2, IgG4, IgG3. Lambda light chains predominate over κ light chains.[38,60]

The epidermal cell surface binding pattern in paraneoplastic pemphigus sera is identical to that seen in pemphigus vulgaris or foliaceus.[38,49,57,67] To distinguish the circulating antibodies from those seen in pemphigus vulgaris, nonstratified and stratified squamous epithelia are used as substrates for indirect immunofluorescence. When indirect immunofluorescence is performed on monkey esophagus (stratified epithelium) and rodent urinary bladder (nonstratified epithelium), autoantibodies from sera of patients with paraneoplastic pemphigus will react with both substrates; sera from patients with pemphigus vulgaris or foliaceus will only react with monkey esophagus.[39] Urinary bladder was chosen as the preferred tissue because it is a complex transitional epithelium with a high density of desmosomes.[57] In the initial study by Anhalt et al,[38] the autoantibodies bound consistently and strongly to the epithelium of urinary bladder, respiratory epithelium, small bowel epithelium, and colon epithelium, and with variable intensity to intercalated disks of myocardium,
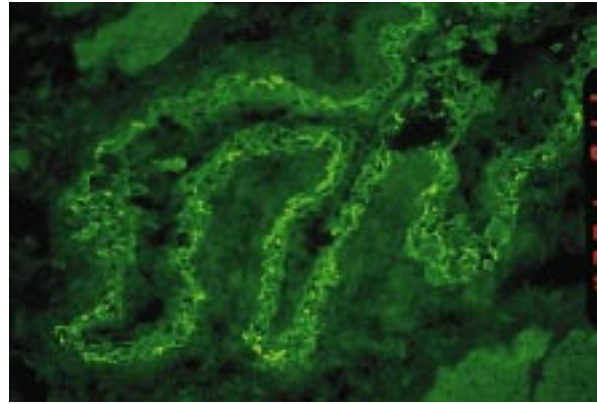

Fig 12. Immunofluorescence findings of paraneoplastic pemphigus. Indirect immunofluorescence demonstrates characteristic cytoplasmic and cell surface staining of rat bladder epithelium by circulating IgG autoantibodies. (Original magnification ×100.)

skeletal muscle, and thyroid epithelium. The most intense binding was observed in the urinary bladder epithelium.

Initially, indirect immunofluorescence on rat bladder epithelium seemed highly reliable, but reports involved only a limited number of patients.[70] Subsequently, reports by Helou, Allbritton, and Anhalt,[57] in a study of 28 patients with paraneoplastic pemphigus, demonstrated a specificity of 83% and a sensitivity of 75% of indirect immunofluorescence studies on rat bladder epithelium. With amplification of the immunofluorescence signal by indirect complement fixation, the sensitivity of the technique was increased to 89%.[57] Studies were also performed on nonepithelial tissues in which desmosomes are present, such as myocardium and liver. Indirect immunofluorescence on liver was specific (96.5%) but insensitive (43%). False-positive results have also been reported.[71] Therefore indirect immunofluorescence on rat bladder epithelium is an adequate screening test for paraneoplastic pemphigus, but is false negative in as many as 25% of patients. Immunoprecipitation must therefore be performed for confirmation of the diagnosis of paraneoplastic pemphigus by identification of the characteristic antigen complex.[57]

TARGET ANTIGENS (Table III, Fig 13)
Pemphigus herpetiformis

The recognition of target antigens has always been a focus of extensive study in pemphigus
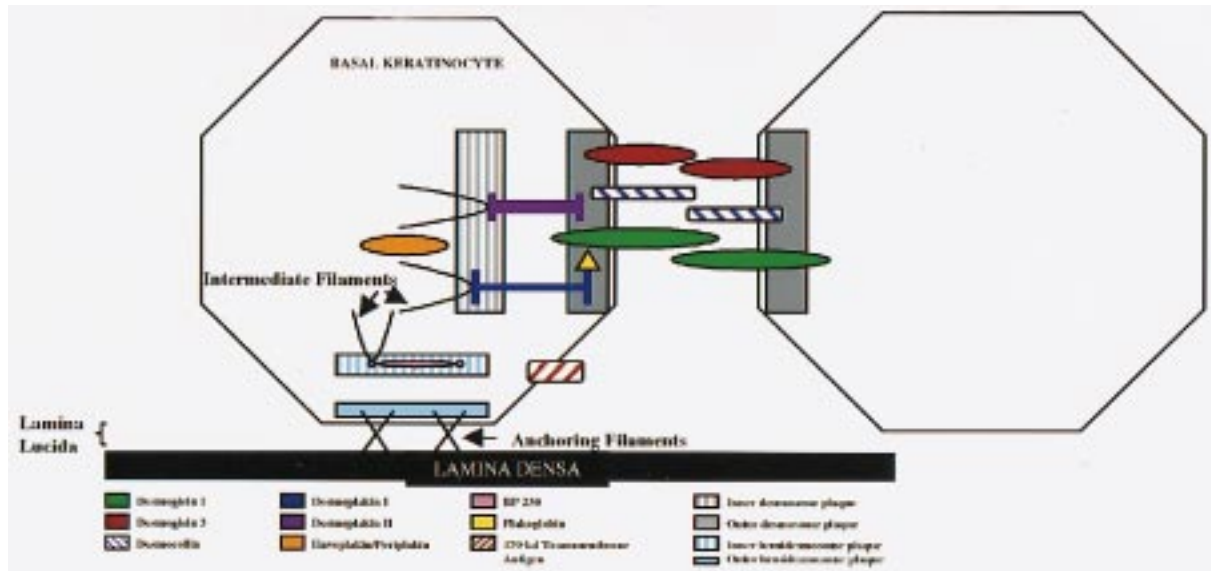
Fig 13. Schematic diagram of the target autoantigens in the new pemphigus variants.[72-76] (Although desmoglein 1 is depicted here in the desmosome of a basal keratinocyte, it is predominantly located in the upper epidermis.)

Table III. Delineated autoantigens for the new pemphigus variants

Disease	Autoantigen	Location	Molecular weight (kd)	Reference No. (s)
Pemphigus herpetiformis	Desmoglein 1 (majority)	Upper epidermis	160	9, 68, 77
	Desmoglein 3	Lower epidermis	130	20, 77
IgA pemphigus IEN type	Desmoglein 3 (one case only)	Lower epidermis	130	31
IgA pemphigus SPD type	Desmocollin 1	Upper epidermis	105-115	30, 32, 35
Paraneoplastic pemphigus	Desmoplakin I	Desmosome	250	38
	Desmoplakin II	Desmosome	~210	60
	Bullous pemphigoid antigen 1 (BP230)	Hemidesmosome	230	38
	Envoplakin	Desmosome	210	81, 83
	Periplakin	Desmosome	190	55, 82, 83
	Undetermined		170	85
	Desmoglein 3	Lower epidermis	130	84
	Desmoglein 1	Upper epidermis	160	84

research. Accumulated evidence from immunoblotting and immunoprecipitation has revealed that the IgG autoantibodies of most patients with pemphigus herpetiformis target the desmosomal component, desmoglein 1 exclusively.[9,68] Because desmoglein 1 is predominantly located in the upper epidermis, this may explain the preferential binding of IgG to the upper epidermis. Immuno-

adsorption studies further confirm the specificity of the IgG autoantibodies.[68]

In 1997, Kubo et al[20] described a patient with pemphigus herpetiformis with reactivity only with desmoglein 3 by immunoblot analysis. Direct and indirect immunofluorescence also demonstrated keratinocyte cell surface staining in the lower layers of the epidermis, where desmoglein 3 is locat-

ed.[20] Thus both desmoglein 1 and desmoglein 3 are recognized by pemphigus herpetiformis autoantibodies.[77]

IgA pemphigus

There are 2 types of desmosomal cadherins: desmoglein and desmocollin, both of which occur as 3 isoforms, desmoglein 1, 2, and 3 and desmocollin 1, 2, and 3, encoded by different genes.[78,79] In 1991, Ebihara et al[30] demonstrated by immunoblotting that serum from a patient with the IEN type of IgA pemphigus reacted exclusively with a 120-kd protein in normal human skin extract and a desmosome-enriched bovine snout epidermis sample. In this study, sera from 3 patients with the SPD type of IgA pemphigus also reacted with a doublet of 115-kd and 105-kd proteins, which appeared to be identical to desmocollins 1 and 2 in the bovine desmosome sample. Years later, Hashimoto, Ebihara, and Nishikawa[32] demonstrated by immunoblotting that IgA antibodies in 10 of 17 IgA pemphigus sera (7 SPD type and 3 IEN type) reacted variously with either bovine desmoglein 1 or desmocollin, not with human desmocollin. The significance of the results of this study was unclear at that time, since no IgA pemphigus sera had been shown to react with human desmocollin by immunoblotting. The reason for this may be that IgA pemphigus sera react with conformation-dependent epitopes on desmocollin, because most pathogenic autoantibodies recognize conformation-sensitive epitopes of desmogleins in pemphigus foliaceus and pemphigus vulgaris.[3,80] Immunoprecipitation is a useful method to detect conformation-dependent epitopes by IgG antibodies, but a robust immunoprecipitation method with IgA antibodies has not yet been established.

More recently, Hashimoto et al[35] have revealed that human desmocollin 1 is an autoantigen for the SPD type of IgA pemphigus. In this study, mammalian expression vectors containing the entire coding sequence of human desmocollin 1, 2, and 3 were constructed and transfected into COS7 cells. Immunofluorescence of the COS7 cells demonstrated that IgA autoantibodies of 6 cases of the SPD type of IgA pemphigus reacted with the surface of cells expressing desmocollin 1 (Fig 14), but not with cells expressing desmocollin 2 or desmocollin 3. None of the 7 cases of the IEN type of IgA pemphigus reacted with cells transfected with any desmocollins. This study also demonstrated that immuno-
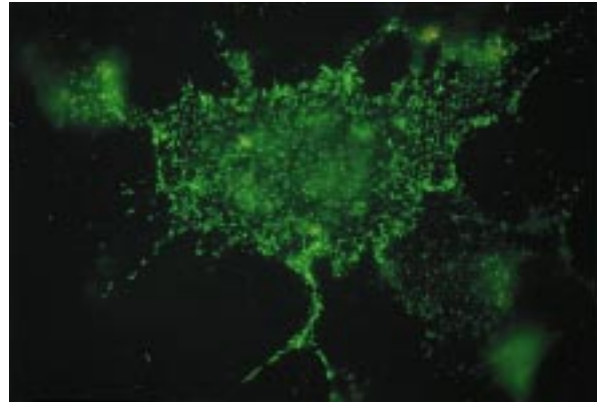

Fig 14. Immunofluorescence findings of the SPD type of IgA pemphigus. Indirect immunofluorescence demonstrates that sera from the SPD type of IgA pemphigus clearly stains the cell surface of COS7 cells transfected with desmocollin 1 in a granular pattern. (Original magnification ×300.)

fluorescence using cells transfected with cDNA encoding antigenic proteins is a useful method for defining antigens whose epitopes are conformation-dependent and therefore cannot be detected with standard immunoblotting techniques.[35]

The target antigen for the IEN type of IgA pemphigus has also recently been identified in 1 patient. Wang et al[31] demonstrated in immunoblotting studies that the IgA autoantibodies of a patient with the IEN type of IgA pemphigus reacted to recombinant desmoglein 3, which is also recognized by IgG autoantibodies from classic pemphigus vulgaris.[4] In the immunoblotting studies, a partially purified baculovirus-expressed recombinant desmoglein 3 protein was used. The specificity of the IgA autoantibodies against desmoglein 3 was further confirmed by immunoadsorption.[31] Others, however, have found no desmoglein 3 or desmoglein 1 reactivities by enzyme-linked immunosorbent assay (ELISA) in 5 patients with the IEN type of IgA pemphigus (Amagai and Hashimoto, unpublished observation). Further studies in large numbers of patients are needed to confirm the target antigen of the IEN type of IgA pemphigus.

Paraneoplastic pemphigus

The paraneoplastic pemphigus autoantigens identified to date include cytoplasmic proteins of the plakin gene family (desmoplakin I and II, bullous pemphigoid antigen 1 [BP230], envoplakin

and periplakin), desmosomal antigens (desmoglein 3 and desmoglein 1), and an undetermined 170-kd transmembranous antigen.[38,60,74,75,81-85] Plakins are molecules that are thought to link the keratin intermediate filaments to the cell surface, specifically to desmosomes and hemidesmosomes.[76,86] In the desmosomes, the known plakins are desmoplakin, envoplakin, and periplakin,[75,76] whereas bullous pemphigoid antigen 1 is the major plaque protein of the epidermal hemidesmosome.[86]

In the initial report by Anhalt et al,[38] the serum of all 5 patients immunoprecipitated an identical complex of 4 polypeptides from human keratinocyte extracts, with estimated molecular weights of 250, 230, 210, and 190 kd. The 210-kd and 190-kd bands were most consistently visualized. A diffuse band at 170 kd was also occasionally visualized, which was suspected to be a degradation product of one of the higher-molecular-weight antigens.[38] The identities of the 250-kd and 230-kd antigens were subsequently determined to be desmoplakin I and bullous pemphigoid antigen 1 (BP230), respectively.[38]

Later, studies identified the 210-kd antigen as desmoplakin II, another major cytoplasmic plaque protein of desmosomes.[60] In the study by Hashimoto et al,[54] immunoblotting of epidermal extracts and bovine desmosome preparations revealed a difference of mobility on the gel between the 210-kd protein detected by paraneoplastic pemphigus sera and desmoplakin II, detected by the anti-desmoplakin monoclonal antibody. These results suggested that the 210-kd antigen was not desmoplakin II, as previously thought.[54] More confirmatory evidence of the difference between desmoplakin II and the 210-kd protein stems from the observation that the 210-kd antigen and desmoplakin I are not always detected simultaneously by the same sera.[54,58] Desmoplakins I and II are known to be produced from the same gene by alternative splicing, and desmoplakin II is a part of desmoplakin I.[87] Therefore, if the 210-kd antigen is desmoplakin II, desmoplakin I and the 210-kd antigen should always be detected simultaneously. The 210-kd antigen, the faster migrating band, was later determined by cDNA cloning and biochemical studies to be envoplakin, which is homologous to desmoplakin and a novel precursor protein of the cornified envelope.[75,81,83] More recently, the 190-kd antigen was identified as periplakin, which is also homologous to desmo-

plakin.[55,74,82,83] The 170-kd antigen is a transmembrane protein, which may be a critical antigen in the pathogenesis of tissue injury in paraneoplastic pemphigus. The 170-kd antigen is now recognized by autoantibodies in almost all cases of paraneoplastic pemphigus, but its true identity has not yet been determined.[39,85] Reports have also suggested that a 130-kd protein recognized by paraneoplastic pemphigus sera may be desmoglein 3 (the target antigen of pemphigus vulgaris).[52,54,88,89]

A recent study by Amagai et al[84] revealed that desmoglein 3 is a key cell surface target antigen in paraneoplastic pemphigus. ELISA using baculovirus-expressed recombinant desmogleins 1 and 3 revealed that 100% of paraneoplastic pemphigus sera tested were positive against desmoglein 3, whereas 64% of sera were also positive against desmoglein 1. All of 12 sera tested immunoprecipitated desmoglein 3.[84] Because autoantibodies against desmogleins have been proven to be pathogenic in passive transfer experiments,[38,39] and desmogleins are extracellularly located and therefore more accessible to immune targeting, they may be more important as the pathogenic target antigens.

PATHOGENESIS
Pemphigus herpetiformis

Anti-desmoglein antibodies in pemphigus herpetiformis induce spongiosis with eosinophil infiltration, but rarely produce acantholysis, in contrast to classical pemphigus.[20] A theory has been proposed to explain why the anti-desmoglein antibodies give rise to different clinical and histologic presentations. It is thought that the autoantibodies in classical pemphigus and in pemphigus herpetiformis recognize different epitopes on the antigen molecules.[20] Autoantibodies in classical pemphigus may inhibit the adhesive function of desmoglein or activate a signaling pathway to induce proteinases, leading to acantholysis.[90,91] Autoantibodies in pemphigus herpetiformis may bind different epitopes and may not inhibit the adhesive function or induce the signaling pathway of proteinases.[20]

In a study by O'Toole et al,[68] biopsy specimens from two patients with pemphigus herpetiformis demonstrate a predominantly neutrophilic infiltration with a co-localization of in vivo–bound IgG and interleukin-8 (IL-8), a potent neutrophil chemoattractant, at the upper epidermis, where
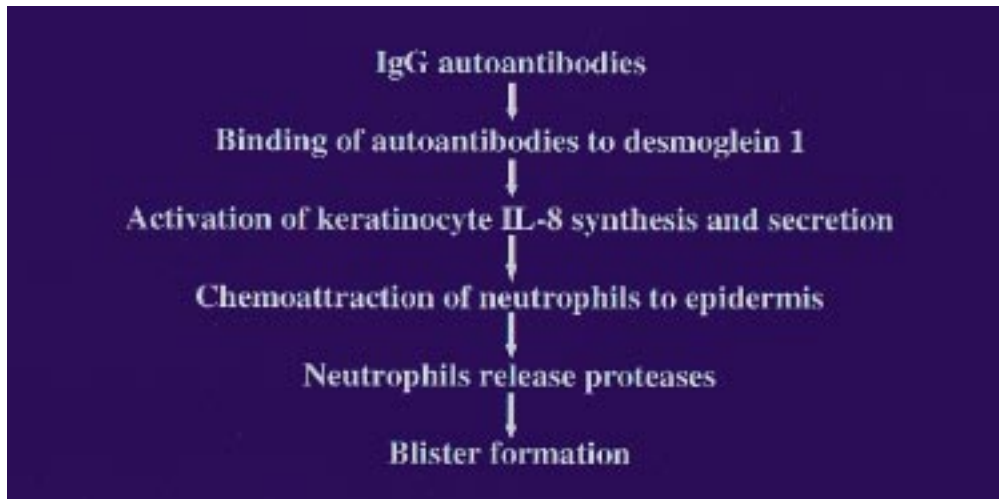
Fig 15. Proposed pathogenesis of neutrophil-dominant pemphigus herpetiformis.

neutrophil infiltration and acantholysis are apparent. This study also demonstrated the in vitro activation of IL-8 cytoplasmic expression and secretion in cultured keratinocytes by the purified IgG of the patients with pemphigus herpetiformis. The keratinocytes treated with this IgG secreted a 5- to 7-fold increase of IL-8 (determined by ELISA) compared with controls. These results suggested that the IgG autoantibodies in pemphigus herpetiformis are responsible for recruiting neutrophils to the upper epidermis by inducing keratinocyte IL-8 secretion (Fig 15).[68]

IgA pemphigus

In 1993, Supapannachart and Mutasim[69] were able to induce intraepidermal acantholysis with two IgA pemphigus (SPD type) serum specimens using skin explant cultures. Immunofluorescence staining showed that the antibody was fixed to the cell surface antigens (3 hours) before the onset of acantholysis (24 hours), suggesting a possible role for the circulating antibody in the induction of acantholysis.[69]

Because desmoglein 3 is a common target antigen for pemphigus vulgaris and a subset of the IEN type of IgA pemphigus, it is unclear why different isotypes of autoantibodies develop toward the same antigen. The generation of antibodies is a complex immunologic process involving T and B lymphocytes. T cells direct the production of antibodies indirectly through effects on the B cells' transformation into plasma cells.[90] Studies have

shown that helper T-cell subset 2 (Th2) is responsible for directing IgA production in mice.[92] These Th2 cells in turn secrete IL-5, which then stimulates B cells to produce IgA.[93] A similar process may be involved with IgA pemphigus (Fig 16).

There are also theories for the prominent neutrophil infiltration present in IgA pemphigus. Recently, the specific binding site for the monocyte/granulocyte IgA-Fc receptor (CD89) has been localized to the constant domain of human IgA1 distal to the hinge region.[94] This arrangement of the binding site may possibly provide resistance to protease degradation, allowing for efficient binding of neutrophils.[95]

It has also been demonstrated that there is an absence of complement deposition in most cases of IgA pemphigus.[22,26,28,69] In the study by Hashimoto et al[26] in 1987, by means of complement-enhancing indirect immunofluorescence testing using anti-C1q, C4, C3, and C5 antiserum, no evidence of complement activation was seen in these IgA antibodies. Junctional deposits of C3 were noted in only 4 of the 29 cases reviewed by Wallach.[22] This may imply that the acantholysis in IgA pemphigus may be complement-independent.

Paraneoplastic pemphigus

The actual cause of paraneoplastic pemphigus has always been a matter of speculation.[39] One theory describes an antitumor immune response that cross-reacts with normal epithelial proteins.[39] This theory is based on similar tumor-associated
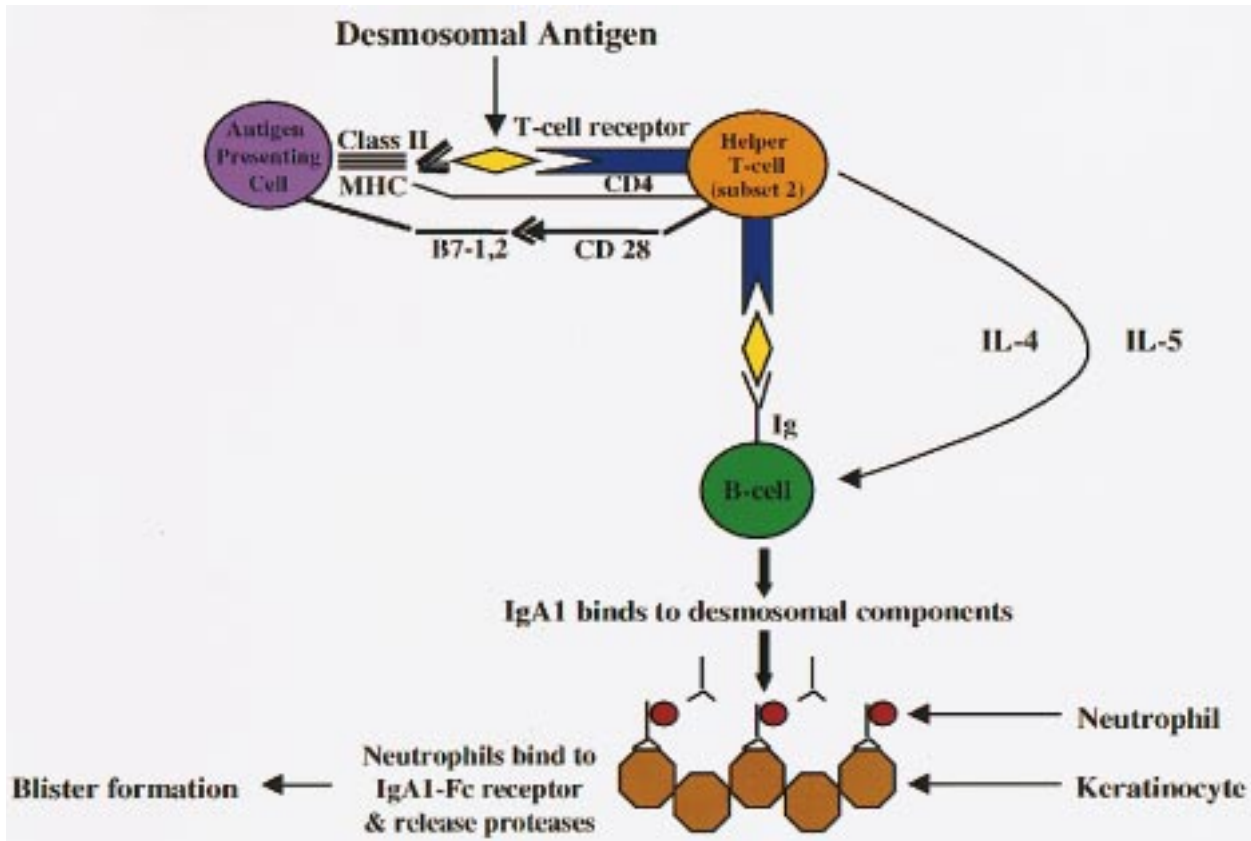
Fig 16. Proposed pathogenesis of IgA pemphigus.

autoimmune phenomena occurring in other organ systems. For example, in certain ovarian carcinomas, the neoplasm may produce a neuroectodermal protein. These patients experience an autoantibody response against the neuroectodermal protein normally present in Purkinje cells in the cerebellum, resulting in ataxia.[96,97] Cancer-associated retinopathy is another similar phenomenon.[39] Certain patients with small cell carcinoma of the lung anomalously express proteins normally found exclusively in the choroid and retina of the eye. These patients developed autoantibodies against this tumor-associated protein and became blind.[98,99] Applying this theory to paraneoplastic pemphigus, it is known that desmoplakins are expressed in thymomas and Castleman's tumors, and it is possible that these patients' autoantibodies were initiated against desmoplakins in these tumors. However, the majority of affected patients have lymphomas or chronic leukemias of B-cell origin, which do not naturally produce desmosomes or express desmoplakins.[60]

Desmosomes and "desmosome-like junctions"

have been known to be anomalously produced by tumors that do not normally possess desmosomes. These tumors include sarcomas, lymphomas, neuroblastomas, and meningiomas.[100-102] Desmoplakins have also been detected by immunostaining in reactive lymph nodes, tonsils, non-Hodgkin's B-cell lymphomas, and synovial sarcomas.[103] These findings can support the hypothesis that these tumors may anomalously produce these antigens and that autoantibodies directed against these tumor antigens become cross-reactive with epithelial antigens, causing the mucocutaneous disease.[60]

Other hypotheses also exist: treatment with cytokines may have induced paraneoplastic pemphigus in a patient with underlying lymphoma or Waldenström's macroglobulinemia.[104] The induction of autoimmunity may be due to a dysregulated cytokine production by tumor cells.[39] In certain cases of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Castleman's disease, the tumors secrete massive amounts of IL-6 in vitro.[105-107] Because IL-6 is known to promote
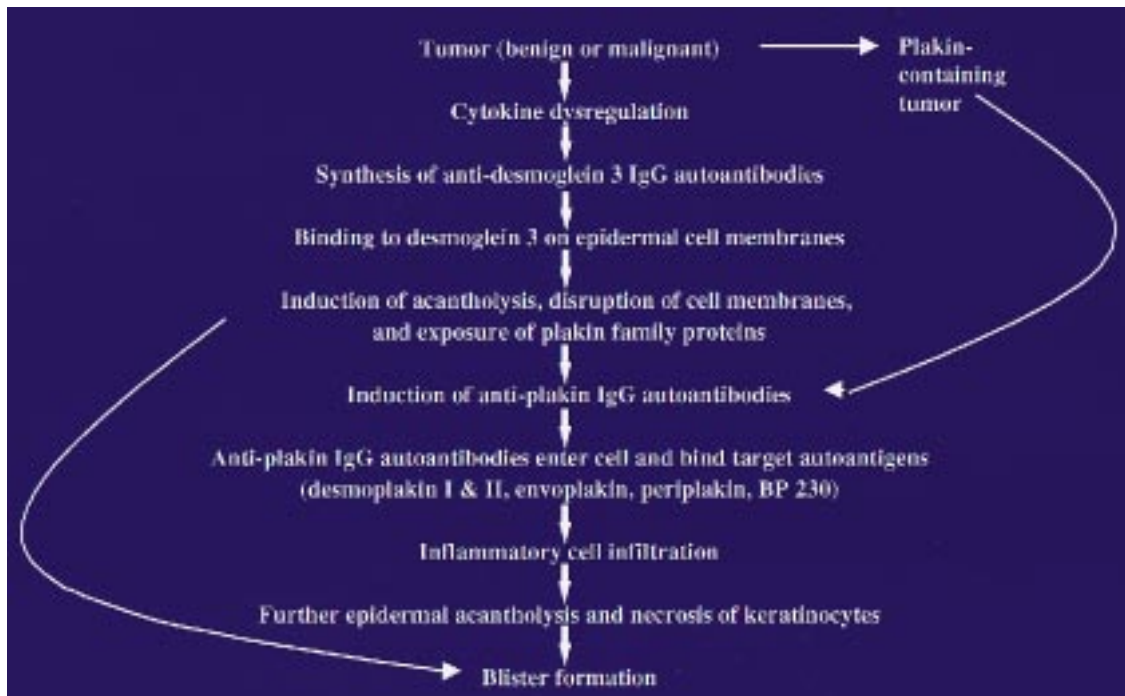
Fig 17. Proposed pathogenesis of paraneoplastic pemphigus.

B-cell differentiation and drive immunoglobulin production, and dysregulated IL-6 production has been demonstrated in certain autoimmune diseases, a link between tumor-associated cytokine over-expression and autoimmunity could exist.[39]

The pathophysiologic relevance of the paraneoplastic pemphigus autoantibodies in the induction of acantholysis and consequent blister formation is now clear. It has been demonstrated that when autoantibodies from paraneoplastic pemphigus sera are injected into neonatal mice, acantholysis and cutaneous blisters are induced, demonstrating that these autoantibodies are pathogenic in paraneoplastic pemphigus, and not merely an epiphenomenon.[38,39] The acantholytic changes are indistinguishable from those observed with passive transfer of pemphigus vulgaris autoantibodies into animals.[39] Ultrastructural examination of the skin of the mice revealed a loss of cell-cell adhesion, but normal basal cell–dermal cell attachment. The epidermal cells also showed mitochondrial swelling and cytoplasmic vacuolization.[38]

Because most of the autoantibodies recognize specific cytoplasmic plaque proteins by immuno-precipitation, questions have been raised as to how these anti-cytoplasmic protein autoantibodies can be directly involved in the induction of acantholy-

sis, since the cytoplasmic location of the autoantigens does not allow circulating antibodies to access them.[84] Thus the pathophysiologic relevance of these anti-plakin autoantibodies is not clear. Amagai et al[84] have recently demonstrated that affinity-purified anti-desmoglein 3 antibodies are pathogenic and cause acantholysis and blister formation in neonatal mice by passive transfer. Removal of the anti-desmoglein 3 antibodies by immunoadsorption eliminated this pathogenic ability of paraneoplastic pemphigus sera. Therefore it is more likely that anti-desmoglein 3 autoantibodies present in these patients initiate the acantholytic process and cause damage to the cell membranes. Once the membrane is damaged, autoantibodies against the plakin family are induced, which then enter the cell and bind the target autoantigens by an epitope spreading phenomenon (Fig 17).[84,108] The possible pathogenic role of autoantibodies against the undetermined 170-kd transmembrane cell surface antigen has been suggested but not been clearly defined.[39,85]

TREATMENT

Because pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus are rare and newly described variants of pemphigus, compre-

hensive studies of large numbers of patients thus far have not taken place. The following summary of treatment options is taken from personal experiences of physician-investigators on small numbers of cases.

Pemphigus herpetiformis

A common problem is the choice of proper treatment. Good results have been demonstrated by combined treatment with dapsone and low doses of systemic corticosteroids, but in several cases, a regimen of corticosteroids in combination with immunosuppressants, such as azathioprine and cyclophosphamide, is necessary.[109]

Dapsone is the drug of first choice for the treatment of pemphigus herpetiformis with doses ranging from 100 to 300 mg daily.[8,11] Dapsone may be given as monotherapy or in combination with systemic corticosteroids and immunosuppressants.[109] Cases of pemphigus with low or negative antibody titers or those demonstrating eosinophilic spongiosis appear more likely to respond to dapsone therapy as well.[109] Sulfapyridine 2 g daily may also be effective.[11]

Systemic corticosteroids, usually in combination with dapsone, sulfapyridine, or immunosuppressive agents, were required to obtain remission in 14 of 15 patients with pemphigus herpetiformis in the study by Maciejowska, Jablonska, and Chorzelski.[8] In the study by Ingber and Feuerman,[11] remission was achieved with low-dose prednisone or dapsone, or both. Prednisone doses used by various physicians ranged from 10 to 120 mg daily for initial control.[8,11]

Immunosuppressive drugs, such as azathioprine and cyclophosphamide, can be added to reduce corticosteroid doses and resulting complications. Azathioprine is the most commonly used immunosuppressive agent, usually as an adjunct to corticosteroids, but occasionally as monotherapy.[109] Azathioprine 100 to 200 mg has been used in combination with prednisone to treat pemphigus herpetiformis, remission obtained in one of two cases.[8] Cyclophosphamide 50 to 100 mg daily, in combination with prednisone, was effective in obtaining remission in 3 patients after failure of other therapy.[8]

Plasmapheresis has been used in an attempt to reduce the titers of pathogenic autoantibodies in patients with pemphigus. It often results in clinical improvement in otherwise therapy-resistant cases of pemphigus. Plasmapheresis should be used in conjunction with other agents to suppress the otherwise inevitable rebound increase in antibody synthesis afterward.[109] In the study by Maciejowska, Jablonska, and Chorzelski,[8] one patient was treated with plasmapheresis in addition to prednisone and cyclophosphamide, resulting in rapid remission. A relapse after 9 months was treated with prednisone and cyclophosphamide, resulting in complete remission.

IgA pemphigus

Dapsone has proved to be the drug of choice in the treatment of IgA pemphigus.[22-25,36,37] With therapeutic doses, dapsone interferes with the myeloperoxidase-hydrogen peroxide, halide-mediated cytotoxic system of neutrophils. This action results in reduced cytotoxicity to adjacent cells.[110] Not surprisingly, dapsone is effective in disorders with prominent neutrophil infiltration. Dapsone was effective in 16 of 23 patients, usually at a dose of 100 mg daily.[22] If dapsone is not well tolerated, sulfapyridine in combination with prednisone or photochemotherapy with PUVA with etretinate are useful alternatives.[27,111]

In some cases the effects of dapsone are either insufficient or only transient[26,112]; therefore etretinate is an excellent second-line treatment. The retinoid derivative etretinate was effective in 4 patients with IgA pemphigus, according to Wallach.[22] Etretinate is thought to act as an anti-inflammatory agent by its inhibition of the migration of monocytes and neutrophils in vivo.[113] Some patients have responded well to a combination of dapsone 50 to 100 mg daily and etretinate 20 to 30 mg daily.[29,112] Other patients may require etretinate to treat subsequent flares.[21,27] Because etretinate is no longer available in the United States, we assume that acitretin may be as effective for these indications.

In the treatment of IgA pemphigus, good results have been achieved with moderate doses of systemic corticosteroids alone in 5 patients and in combination with immunosuppressive agents in 2 patients.[22] The suggested corticosteroid dose is 0.5 to 1 mg/kg daily. Topical corticosteroid therapy may also be adequate in some cases of IgA pemphigus. It is also an extremely useful adjuvant to systemic therapy when disease is more severe, permitting a reduction in requirements for corticosteroid therapy.[109] The patient described by Wang

et al[31] was treated with mid-potency topical steroids for several weeks, with resolution of lesions and no recurrence of disease 3 months after discontinuation of therapy.

Azathioprine is a commonly used immunosuppressant in pemphigus, but does not seem to be effective in treating IgA pemphigus. In combination with fluocortolone 80 mg daily, azathioprine 150 mg daily was used in the treatment of one patient without benefit.[29] PUVA, alone or in combination with etretinate, was effective in 3 patients with IgA pemphigus.[22,27] Colchicine was also effective in one of two patients with IgA pemphigus.[22] Aggressive therapy with plasmapheresis, prednisone, and cyclophosphamide has also been used for a recurrence after initial treatment with dapsone and prednisone.[33]

Paraneoplastic pemphigus

Patients with paraneoplastic pemphigus and benign tumors, such as thymomas or Castleman's tumors, should have the tumor surgically excised. The majority of these patients will either improve substantially or clear completely.[38,39,52,53,59,67] Complete resolution of lesions usually occurs 6 to 18 months after excision of a benign neoplasm.[39,59] In the one patient presented by Jansen, Plewig, and Anhalt,[59] progressive mucocutaneous lesions proved refractory to high-dose corticosteroids, aromatic retinoids, and immunosuppression. After surgical removal of a Castleman's tumor, there was complete resolution of all symptoms with no recurrences for more than 3 years.

Regarding malignant neoplasms, there is no consensus on a standard effective therapeutic regimen.[39] Cutaneous lesions respond more quickly to therapy, whereas stomatitis is generally refractory to most forms of therapy.[39] Induction of chemotherapy has occasionally resulted in complete resolution of the malignancy (a diffuse large-cell lymphoma and a T-cell lymphoblastic lymphoma) and a slow resolution of the skin lesions.[56,58] In general, corticosteroids produce only partial resolution of lesions.[38,39,114] Dega et al[50] presented a patient with Hodgkin's lymphoma in remission and an atypical presentation of paraneoplastic pemphigus, absence of mucosal involvement. After treatment with oral prednisone 1 mg/kg daily, the skin lesions cleared completely, with the patient still free of disease 18 months after diagnosis. This favorable outcome with corticosteroid use alone in this case is unusual and may be due to the lack of adverse prognostic factors, such as severe mucosal involvement and a progressive underlying cancer.[50]

Other attempted treatments that are generally unsuccessful include immunosuppression with cyclophosphamide or azathioprine, cyclosporine, gold, dapsone, plasmapheresis, and photopheresis.[38-41,44,47,51,63] Only a few successful outcomes have been described. Krunic et al[46] described a patient with an encapsulated round-cell liposarcoma who, after tumor resection and administration of prednisone (0.75-1.0 mg/kg) and azathioprine (100 mg/day), experienced a significant reduction of skin lesions in 2 weeks and a gradual healing of oral lesions. Another patient treated with prednisone 40 mg and azathioprine 100 mg daily experienced complete resolution of skin lesions and marked alleviation of the stomatitis with only residual ulceration of the tongue 2 years after diagnosis.[44] The combination of oral cyclosporine 5 mg/kg daily and prednisone 35 mg daily has also been reported to heal erosions of the mucous membranes substantially within 2 months in a patient with chronic lymphocytic leukemia.[63]

Izaki et al[61] reported a potential therapeutic effect of plasmapheresis in a patient with paraneoplastic pemphigus and chronic lymphocytic leukemia. The treatment resulted in a decrease in the antibody titer from 1:640-1280 to 1:20-40, as well as some clearing of the skin and mucosal lesions. Two other patients described in the literature also received plasmapheresis therapy, in combination with systemic prednisone, experiencing significant clearing of skin and mucosal lesions.[43,115] Schoen et al[62] recently described a patient with paraneoplastic pemphigus and an inflammatory myofibroblastic tumor who showed only minimal improvement after excision of the neoplasm and administration of corticosteroids. An immunoapheresis regimen was then initiated using sheep anti-human-IgG bead-formed agarose gel, leading to disappearance of circulating autoantibodies and the patient's recovery. Postapheresis of high-dose immunoglobulin was administered to prevent autoantibody resynthesis.[62]

CLINICAL COURSE AND PROGNOSIS
Pemphigus herpetiformis

The most significant observation in the follow-up of patients with pemphigus herpetiformis is the

benign course of the disease. The disease responds well to treatment with a tendency to achieve complete remission and is controlled with a low dose of steroids.[11] Some physicians observed that the classic features of pemphigus foliaceus, or occasionally pemphigus vulgaris, will eventually develop in many patients with pemphigus herpetiformis. In some cases, after treatment has been discontinued, the cutaneous lesions transform into a pemphigus foliaceus phenotype.[8,9] Once this transformation occurs, the treatment regimen should include corticosteroids and immunosuppressive drugs. In the study by Maciejowska, Jablonska, and Chorzelski,[8] the presence of detectable circulating autoantibodies in pemphigus herpetiformis also appears to be associated with greater resistance to therapy.

IgA pemphigus

A follow-up study up to a maximum of 22 years has determined that IgA pemphigus carries a chronic, benign course and responds well to appropriate therapy.[22] IgA pemphigus, as a superficial blistering disease, usually heals without scarring, if appropriate treatment is provided.[31] The milder clinical presentation and benign course may also be explained by the lower IgA autoantibody titer and the inability of IgA to activate complement by the classical pathway.[31] Recurrences of lesions have been noted after termination of treatment or reduction in drug dosage.[26]

IgA pemphigus is also associated with other medical disorders. In the cases reviewed by Wallach[22] in 1992, 6 of the 29 patients had an associated monoclonal gammopathy. This gammopathy was of the IgA class with κ light chains in 5 of the 6 patients. Two gammopathies were benign; one patient had a B-cell lymphoma, and two patients had myeloma. In two patients, the monoclonal gammopathy developed only years after the onset of the dermatosis.[22] In those cases with an associated malignant IgA gammopathy, the prognosis was related to the malignancy.[29] Gastrointestinal diseases may also be associated with IgA pemphigus. One case each of Crohn's disease and gluten-sensitive enteropathy have been reported in the literature.[22]

Paraneoplastic pemphigus

As stated earlier, in patients with paraneoplastic pemphigus and benign neoplasms, the disease generally clears substantially or goes into complete remission once the neoplasm is surgically excised.[39] Follow-up serology has shown a reduction in levels of circulating antibodies against the paraneoplastic pemphigus antigens by more than 90%.[39] Reported cases of paraneoplastic pemphigus with malignant neoplasms have generally followed a rapidly progressive and invariably fatal course.[38,39,67] Anhalt[39] reported that 30 of 33 patients with malignancies died of complications of the syndrome or of treatment 1 month to 2 years after diagnosis. Two rare cases of prolonged survival, both associated with chronic lymphocytic leukemia, have been described: one patient was still alive 3 years after the onset of disease[44]; the other patient died nearly 8 years after the onset of paraneoplastic pemphigus.[63]

The disease course does not parallel that of the underlying malignancy and has even occurred in patients apparently cured of their malignancy.[39,43] In 1 case, paraneoplastic pemphigus developed after successful autologous bone marrow transplantation for non-Hodgkin's lymphoma. The patient was free of detectable tumor by autopsy, but died of respiratory complications of paraneoplastic pemphigus.[43] The mucosal disease is particularly refractory and often progresses to involve the respiratory tract, resulting in respiratory failure.[114]

Of the patients who have not survived, death is usually secondary to sepsis, gastrointestinal bleeding, multiple organ failure, or respiratory failure.[39] Patients with autoimmune disease associated with B-cell neoplasms tend to have a high incidence of autoimmune cytopenias, often predisposing them to subsequent sepsis.[39] Anhalt[39] reported that 6 of 33 patients died of pulmonary failure and had severe hypoxia with a relatively clear chest roentgenogram before death. The patient described by Fullerton et al[43] with pulmonary involvement received a bronchial biopsy before death, which revealed IgG deposition in the intercellular spaces of the bronchial epithelium in vivo. Considering that the autoantibodies of paraneoplastic pemphigus react with desmoplakins and desmoplakins are present in respiratory epithelium, it is possible that the respiratory failure may have been due to autoantibody-mediated injury to bronchial epithelium, resulting in plugging of terminal alveoli and ventilation/perfusion abnormalities.[39]

COMPLICATIONS OF TREATMENT
Systemic corticosteroids

Systemic corticosteroids are the most useful drugs in treating the common forms of pemphigus, rapidly inducing remission in the majority of patients. After their introduction in the 1950s, there was a dramatic decline in mortality; however, the complications of corticosteroids caused by the prolonged high-maintenance doses resulted in significant morbidity.[116-118] The most common complications of prolonged corticosteroid use are quite extensive: hypertension, diabetes mellitus, pancreatitis, peptic ulcers, opportunistic infections, mood alteration, psychosis, hirsutism, osteoporosis, aseptic necrosis of the femoral and humoral heads, abdominal striae, menstrual irregularity, truncal and facial obesity, hypothalamus-pituitary-adrenal axis suppression, cataracts, glaucoma, purpura, hypopigmentation, cutaneous atrophy, impaired wound healing, and proximal myopathy. Routine biochemistry, urinalysis, and determinations of blood pressure and weight should be performed at regular intervals. Bone densitometry, especially in postmenopausal women, should be performed at 1- to 2-year intervals. Ophthalmologic examinations should be performed regularly to screen for cataracts and glaucoma.[119]

Azathioprine

The side effects of azathioprine include teratogenicity, idiopathic hepatitis, increased susceptibility to infection secondary to a dose-dependent bone marrow depression, and an increased risk of internal and cutaneous malignancy. Patients should undergo urinalysis, complete blood cell count, renal and liver function tests, and determination of electrolyte levels before starting therapy and at regular intervals as long as therapy is continued.[120]

Cyclophosphamide

Complications of cyclophosphamide include nausea, vomiting, alopecia, sterility, teratogenicity, hemorrhagic cystitis, bone marrow depression, and an increased risk of internal malignancy. Patients should be monitored as for azathioprine, but with the addition of urinalysis weekly for the first 8 to 12 weeks, then every 2 weeks thereafter.[120]

Dapsone and sulfonamides

Side effects of dapsone include anorexia, nausea, vomiting, hepatic damage, mood changes, exfoliative dermatitis, cutaneous hypersensitivity reactions, and dose-related methemoglobinemia and hemolysis.

Cimetidine may be given to improve gastrointestinal tolerance to dapsone. Baseline and initially weekly laboratory tests should include a complete blood cell count, renal and liver function tests, and determination of electrolyte levels. Glucose-6-phosphate dehydrogenase deficiency must be excluded before therapy. Evaluation of methemoglobin levels can be obtained as clinically indicated.[121-123] The sulfonamides may cause gastrointestinal symptoms, drug-induced rashes, blood dyscrasias, and renal failure.[124]

Plasmapheresis

Potential complications with plasmapheresis include maintaining venous access, a tendency to bleed, electrolyte imbalances, pulmonary edema, allergic reactions, fever, chills, hypotension, and septicemia. Frequent monitoring of vital signs and cardiac monitoring is required during the procedure. Weekly coagulation studies, liver function tests, hepatitis serology, and determination of electrolyte levels should also be performed.[125,126]

REFERENCES

1. Thivolet J. Pemphigus: past, present and future. Dermatology 1994;189(suppl 2):26-9.
2. Dugan EM, Anhalt G, Diaz LA. Pemphigus. In: Jordan RE, editor. Immunologic diseases of the skin. Norwalk (CT): Appleton & Lange; 1991. p. 279-91.
3. Amagai M, Hashimoto T, Green KJ, Shimizu N, Nishikawa T. Antigen-specific immunoadsorption of pathogenic autoantibodies in pemphigus foliaceus. J Invest Dermatol 1995;104:895-901.
4. Amagai M, Klaus-Kovtum V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. Cell 1991;67:869-77.
5. Amagai M, Koch PJ, Nishikawa T, Stanley JR. Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. J Invest Dermatol 1996;106:351-5.
6. Jablonska S, Chorzelski T, Beutner E, Chorzelska J. Herpetiform pemphigus, a variable pattern of pemphigus. Int J Dermatol 1975;14:353-9.
7. Floden CH, Gentale H. A case of clinically typical dermatitis herpetiformis (M. Duhring) presenting acantholysis. Acta Derm Venereol (Stockh) 1955;35:128.

8. Maciejowska E, Jablonska S, Chorzelski T. Is pemphigus herpetiformis an entity? Int J Dermatol 1987;26:571-7.

9. Santi CG, Maruta CW, Aoki V, Sotto MN, Rivitti EA, Diaz LA, et al. Pemphigus herpetiformis is a rare clinical expression of nonendemic pemphigus foliaceus, fogo selvagem, and pemphigus vulgaris. J Am Acad Dermatol 1996;34:40-6.

10. Huhn KM, Tron VA, Nguyen N, Trotter MJ. Neutrophilic spongiosis in pemphigus herpetiformis. J Cutan Pathol 1996;23:264-9.

11. Ingber A, Feuerman EJ. Pemphigus with characteristics of dermatitis herpetiformis: a long-term follow-up of five patients. Int J Dermatol 1986;25:575-9.

12. Beissert S, Metze D, Luger TA, Schwarz T. Pemphigus herpetiformis. Hautarzt 1993;44:594-7.

13. Passarini B, Palmerio B, Costa AM, Neri I. Pemfigo erpetiforme: descrizione di un caso. G Ital Dermatol Venereol 1989;124:411-3.

14. Mutevelic-Arslanagic N, Bokonjic M, Sehic C, Ganic F. Pemphigus herpetiformis (gerpetiformnyi pemfigus). Vestn Dermatol Venerol 1989;10:72-4.

15. Weidner GO, Kleinhans D. Pemphigus herpetiformis. Z Hautkr 1984;59:1663-8.

16. Skripkin IuK, Butov IuS, Khamaganova AV. Gerpetiformnyi pemfigus u dvukh bol'nykh. Vestn Dermatol Venerol 1984;5:43-5.

17. Bauer R, Stadler R, Immel C, Orfanos CE. Akantholyse und eosinophile Spongiose: Pemphigus herpetiformis. Erfolgreiche Retinoidtherapie. Hautarzt 1983;34:13-7.

18. Bauer R, Orfanos CE. Pemphigus herpetiformis: eine klinische Variante des Pemphigus vulgaris. Hautarzt 1980;31:540-4.

19. Micali G, Musumeci ML, Nasca MR. Epidemiologic analysis and clinical course of 84 consecutive cases of pemphigus in eastern Sicily. Int J Dermatol 1998;37:197-200.

20. Kubo A, Amagai M, Hashimoto T, Doi T, Higashiyama M, Hashimoto K, et al. Herpetiform pemphigus showing reactivity with pemphigus vulgaris antigen (desmoglein 3). Br J Dermatol 1997;137:109-13.

21. Wallach D, Foldes C, Cottenot F. Pustulose sous-cornee, acantholyse superficielle et IgA monoclonale. Ann Dermatol Venereol 1982;109:959-63.

22. Wallach D. Intraepidermal IgA pustulosis. J Am Acad Dermatol 1992;27:993-1000.

23. Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. Br J Dermatol 1979;100:61-8.

24. Beutner EH, Chorzelski TP, Wilson RM, Kumar V, Michel B, Helm F, et al. IgA pemphigus foliaceus: report of two cases and a review of the literature. J Am Acad Dermatol 1989;20:89-97.

25. Huff JC, Golitz LE, Kunke KS. Intraepidermal neutrophilic IgA dermatosis. N Engl J Med 1985;313:1643-5.

26. Hashimoto T, Inamoto N, Nakamura K, Nishikawa T. Intercellular IgA dermatosis with clinical features of subcorneal pustular dermatosis. Arch Dermatol 1987;123:1062-5.

27. Tagami H, Iwatsuki K, Iwase Y, Yamada M. Subcorneal pustular dermatosis with vesiculo-bullous eruption: demonstration of subcorneal IgA deposits and a leukocyte chemotactic factor. Br J Dermatol 1983;109:581-7.

28. Hodak E, David M, Ingber A, Rotem A, Hazaz B, Shamai-Lubovitz O, et al. The clinical and histopathological spectrum of IgA-pemphigus: report of two cases. Clin Exp Dermatol 1990;15:433-7.

29. Zillikens D, Miller K, Hartmann AA, Burg G. IgA pemphigus foliaceus: a case report. Dermatologica 1990;181:304-7.

30. Ebihara T, Hashimoto T, Iwatsuki K, Takigawa M, Ando M, Ohkawara A, et al. Autoantigens for IgA anti-intercellular antibodies of intercellular IgA vesiculopustular dermatosis. J Invest Dermatol 1991;97:742-5.

31. Wang J, Kwon J, Ding X, Fairley JA, Woodley DT, Chan LS. Nonsecretory IgA1 autoantibodies targeting desmosomal component desmoglein 3 in intraepidermal neutrophilic IgA dermatosis. Am J Pathol 1997;150:1901-7.

32. Hashimoto T, Ebihara T, Nishikawa T. Studies of autoantigens recognized by IgA anti-keratinocyte cell surface antibodies. J Dermatol Sci 1996;12:10-7.

33. Chorzelski TP, Beutner EH, Kowalewski C, Olszewska M, Maciejowska E, Seferowicz E, et al. IgA pemphigus foliaceus with a clinical presentation of pemphigus herpetiformis. J Am Acad Dermatol 1991;24:839-44.

34. Lutz ME, Daoud MS, McEvoy MT, Gibson LE. Subcorneal pustular dermatosis: a clinical study of ten patients. Cutis 1998;61:203-8.

35. Hashimoto T, Kiyokawa C, Mori O, Miyasato M, Chidgey MAJ, Garrod DR, et al. Human desmocollin 1 (Dsc 1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. J Invest Dermatol 1997;109:127-31.

36. Weston WL, Friednash M, Hashimoto T, Seline P, Huff JC, Morelli JG. A novel childhood pemphigus vegetans variant of intraepidermal neutrophilic IgA dermatosis. J Am Acad Dermatol 1998;38:635-8.

37. Teraki Y, Amagai N, Hashimoto T, Kusunoki T, Nishikawa T. Intercellular IgA dermatosis of childhood: selective deposition of monomer IgA1 in the intercellular space of the epidermis. Arch Dermatol 1991;127:221-4.

38. Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M. Paraneoplastic pemphigus: an autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990;323:1729-35.

39. Anhalt GJ. Paraneoplastic pemphigus. Adv Dermatol 1997;12:77-96.

40. Camisa C, Helm TN. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. Arch Dermatol 1993;129:883-6.

41. Ostezan LB, Fabré VC, Caughman SW, Swerlick RA, Korman NJ, Callen JP. Paraneoplastic pemphigus in the absence of a known neoplasm. J Am Acad Dermatol 1995;33:312-5.

42. Fried R, Lynfield Y, Vitale P, Anhalt G. Paraneoplastic pemphigus appearing as bullous pemphigoid-like eruption after palliative radiation therapy. J Am Acad Dermatol 1993;29:815-7.

43. Fullerton SH, Woodley DT, Smoller BR, Anhalt GJ. Paraneoplastic pemphigus with autoantibody deposition in bronchial epithelium after autologous bone marrow transplantation. JAMA 1992;267:1500-2.

44. Camisa C, Helm TN, Liu YC, Valenzuela R, Allen C, Bona S, et al. Paraneoplastic pemphigus: a report of three cases including one long-term survivor. J Am Acad Dermatol 1992;27:547-53.

45. Plewig G, Jansen T, Jungblut RM, Roher HD. Castleman tumor, lichen planus, and pemphigus vulgaris: Paraneoplastic association of immunologic disease? Hautarzt 1990;41:662-70.

46. Krunic ALJ, Kokai D, Bacetic B, Kesic V, Nikolic MM, Petkovic S, et al. Retroperitoneal round-cell liposarcoma

associated with paraneoplastic pemphigus presenting as lichen planus pemphigoides-like eruption. Int J Dermatol 1997;36:526-9.

47. Stevens SR, Griffiths CEM, Anhalt GJ, Cooper KD. Paraneoplastic pemphigus presenting as a lichen planus pemphigoides-like eruption. Arch Dermatol 1993;129:866-9.

48. Lam S, Stone MS, Goeken JA, Massicotte SJ, Smith AC, Folberg R, et al. Paraneoplastic pemphigus, cicatricial conjunctivitis, and acanthosis nigricans with patchy dermatoglyphy in a patient with bronchogenic squamous cell carcinoma. Ophthalmology 1992;99:108-13.

49. Mutasim DF, Pelc NJ, Anhalt GJ. Paraneoplastic pemphigus. Dermatol Clin 1993;11:473-81.

50. Dega H, Laporte JL, Joly P, Gabarre J, André C. Paraneoplastic pemphigus associated with Hodgkin's disease. Br J Dermatol 1998;138:196-7.

51. Schlesinger T, McCarron K, Camisa C, Anhalt G. Paraneoplastic pemphigus occurring in a patient with B-cell non-Hodgkin's lymphoma. Cutis 1998;61:94-6.

52. Chiewchanvit S, Hashimoto T, Chaiwun B, Nishikawa T. A pemphigus case with long term survival, implicating the spectrum between paraneoplastic pemphigus and pemphigus vulgaris. Int J Dermatol 1997;36:957-8.

53. Lemon MA, Weston WL, Huff JC. Childhood paraneoplastic pemphigus associated with Castleman's tumour. Br J Dermatol 1997;136:115-7.

54. Hashimoto T, Amagai M, Watanabe K, Chorzelski TP, Bhogal BS, Black MM, et al. Characterization of paraneoplastic pemphigus autoantigens by immunoblot analysis. J Invest Dermatol 1995;104:829-34.

55. Borradori L, Trueb RM, Jaunin F, Limat A, Favre B, Saurat JH. Autoantibodies from a patient with paraneoplastic pemphigus bind periplakin, a novel member of the plakin family. J Invest Dermatol 1998;111:338-40.

56. Herrada J, Phillips DK, Hebert AA, Cabanillas F, Jordon RE. A progressive blistering eruption in a patient with lymphoma. Arch Dermatol 1997;133:97, 100-1.

57. Helou J, Allbritton J, Anhalt GJ. Accuracy of indirect immunofluorescence testing in the diagnosis of paraneoplastic pemphigus. J Am Acad Dermatol 1995;32:441-7.

58. Rybojad M, Leblanc T, Flageul B, Bernard PH, Morel P, Schaison G, et al. Paraneoplastic pemphigus in a child with a T-cell lymphoblastic lymphoma. Br J Dermatol 1993;128:418-22.

59. Jansen T, Plewig G, Anhalt GJ. Paraneoplastic pemphigus with clinical features of erosive lichen planus associated with Castleman's tumor. Dermatology 1995;190:245-50.

60. Oursler JR, Labib RS, Ariss-Abdo L, Burke T, O'Keefe EJ, Anhalt GJ. Human autoantibodies against desmoplakins in paraneoplastic pemphigus. J Clin Invest 1992;89:1775-82.

61. Izaki S, Yoshizawa Y, Kitamura K, Kato H, Hashimoto H, Korman NJ, et al. Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. Br J Dermatol 1996;134:987-9.

62. Schoen H, Foedinger D, Derfler K, Amann G, Rappersberger K, Stingl G, et al. Immunoapheresis in paraneoplastic pemphigus. Arch Dermatol 1998;134:706-10.

63. Perniciaro C, Kuechle MK, Colon-Otero G, Raymond MG, Spear KL, Pittelkow MR. Paraneoplastic pemphigus: a case of prolonged survival. Mayo Clin Proc 1994;69:851-5.

64. Castleman B, Iversen L, Menendez V. Localized medi-

astinal lymph node hyperplasia resembling thymoma. Cancer 1956;9:822-30.

65. Keller AR, Hochholzer L, Castleman B. Hyaline vascular and plasma cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972;29:670-83.

66. Carrington PA, Anderson H, Harris M, Walsh SE, Houghton JB, Morgenstern GR. Autoimmune cytopenias in Castleman's disease. Am J Clin Pathol 1990;94:101-4.

67. Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. Arch Dermatol 1992;128:1091-5.

68. O'Toole EA, Mak LL, Guitart J, Hashimoto T, Amagai M, Woodley DT, et al. Activation of interleukin-8 secretion in pemphigus herpetiformis epidermis by anti-desmoglein 1 IgG autoantibodies [abstract]. J Invest Dermatol 1998;110:509.

69. Supapannachart N, Mutasim DF. The distribution of IgA pemphigus antigen in human skin and the role of IgA anti-cell surface antibodies in the induction of intraepidermal acantholysis. Arch Dermatol 1993;129:605-8.

70. Liu AY, Valenzuela R, Helm TN, Camisa C, Melton AL, Bergfeld WF. Indirect immunofluorescence on rat bladder transitional epithelium: a test with high specificity for paraneoplastic pemphigus. J Am Acad Dermatol 1993;28:696-9.

71. Fodinger D, Bocskor B, Wolff K, Rappersberger K. Erythema multiforme: demonstration of autoantibodies against desmoplakin I [abstract]. Clin Res 1993;41:419A.

72. Kowalczyk AP, Bornslaeger EA, Norvell SM, Palka HL, Green KJ. Desmosomes: intercellular adhesive junctions specialized for attachment of intermediate filaments. Int Rev Cytol 1999;185:237-302.

73. Moll R, Moll I. Epidermal adhesion molecules and basement membrane components as target structures of autoimmunity. Virchows Arch 1998;432:487-504.

74. Ruhrberg C, Hajibagheri MA, Parry DA, Watt FM. Periplakin, a novel component of cornified envelopes and desmosomes that belongs to the plakin family and forms complexes with envoplakin. J Cell Biol 1997;139:1835-49.

75. Ruhrberg C, Hajibagheri MA, Simon M, Dooley TP, Watt FM. Envoplakin, a novel precursor of the cornified envelope that has homology to desmoplakin. J Cell Biol 1996;134:715-29.

76. Ruhrberg C, Watt FM. The plakin family: versatile organizers of cytoskeletal architecture. Curr Opin Genet Dev 1997;7:392-7.

77. Ishii K, Amagai M, Komai A, Ebihara T, Chorzelski TP, Nishikawa T, et al. Desmoglein 1 and desmoglein 3 as autoimmune target of herpetiform pemphigus [abstract]. J Invest Dermatol 1998;110:510A.

78. Amagai M. Adhesion molecules I: Keratinocyte-keratinocyte interactions; cadherins and pemphigus. J Invest Dermatol 1995;104:146-52.

79. Buxton RS, Cowin P, Franke WW, Garrod DR, Green KH, King IA, et al. Nomenclature of the desmosomal cadherins. J Cell Biol 1993;121:481-3.

80. Amagai M, Hashimoto T, Shimizu N, Nishikawa T. Absorption of pathogenic autoantibodies by the extracellular domain of pemphigus vulgaris antigen (Dsg 3) produced by baculovirus. J Clin Invest 1994;94:59-67.

81. Kim SC, Kwon YD, Lee IJ, Lee IJ, Chang SN, Lee TG. cDNA cloning of the 210-kDa paraneoplastic pemphigus antigen reveals that envoplakin is a component of the antigen complex. J Invest Dermatol 1997;109:365-9.

82. Mahoney MG, Aho S, Uitto J, Stanley JR. The members of the plakin family of proteins recognized by paraneoplastic pemphigus antibodies include periplakin. J Invest Dermatol 1998;111:308-13.

83. Kiyokawa C, Ruhrberg C, Nie Z, Karashima T, Mori O, Nishikawa T, et al. Envoplakin and periplakin are components of the paraneoplastic pemphigus antigen complex. J Invest Dermatol 1998;111:1236-8.

84. Amagai M, Nishikawa T, Nousari HC, Anhalt GJ, Hashimoto T. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. J Clin Invest 1998;102:775-82.

85. Anhalt GJ, Hilu J, Takehara K, Lee A, Casciola-Rosen L. Identification of a putative transmembrane autoantigen in paraneoplastic pemphigus [abstract]. Clin Res 1993;41:407A.

86. Stanley JR. Cell adhesion molecules as targets of autoantibodies in pemphigus and pemphigoid, bullous diseases due to defective epidermal cell adhesion. Adv Immunol 1993;53:291-325.

87. Green KJ, Parry DA, Steinert PM, Virata ML, Wagner RM, Angst BD, et al. Structure of the human desmoplakins: implications for function in the desmosomal plaque. J Biol Chem 1990;265:2603-12.

88. Joly P, Thomine E, Gilbert D, Verdier S, Delpech A, Prost C, et al. Overlapping distribution of autoantibody specificities in paraneoplastic pemphigus and pemphigus vulgaris. J Invest Dermatol 1994;103:65-72.

89. Hashimoto T, Amagai M, Wang N, Nishikawa T, Karashima T, Moria O, et al. Novel non-radioisotope immunoprecipitation studies indicate involvement of pemphigus vulgaris antigen in paraneoplastic pemphigus. J Dermatol Sci 1998;17:132-9.

90. Morioka S, Naito K, Ogawa H. The pathogenic role of pemphigus antibodies and proteinase in epidermal acantholysis. J Invest Dermatol 1981;76:337-41.

91. Hashimoto K, Shafran KM, Webber PS, Lazarus GS, Singer KH. Anti-cell surface pemphigus autoantibody stimulates plasminogen activator activity of human epidermal cells: a mechanism for the loss of epidermal cohesion and blister formation. J Exp Med 1983;157:259-72.

92. Coffman RL, Seymour BWP, Lebman DA. The role of helper T cell products in mouse B cell differentiation and isotype regulation. Immunol Rev 1988;102:5-28.

93. Coffman RL, Shrader B, Carty T, Mosmann TR, Bond MW. A mouse T cell product that preferentially enhances IgA production. I. Biologic characterization. J Immunol 1987;139:3685-90.

94. Carayannopoulos L, Hexham JM, Capra JD. Localization of the binding site for monocyte IgA-Fc receptor (CD89) to the domains boundary between Cγ2 and Cγ3 in human IgA1. J Exp Med 1996;183:1579-86.

95. Weisbart RH, Kacena A, Schuh A, Golde DW. GM-CSF induces human neutrophil IgA-mediated phagocytosis by an IgA Fc receptor activation mechanism. Nature 1988;332:647-8.

96. Brashear HR, Greenlee JE, Jaeckle KA, Rose JW. Anticerebellar antibodies in neurologically normal patients with ovarian neoplasms. Neurology 1989;39:1605-9.

97. Furneaux HM, Rosenblum MK, Dalmau J, Wong E, Woodruff P, Graus F, et al. Selective expression of Purkinje-cell antigens in tumor tissue from patients with paraneoplastic cerebellar degeneration. N Engl J Med 1990;322:1844-51.

98. Thirkill CE, Fitzgerald P, Sergott RC, Roth AM, Tyler NK, Keltner JL. Cancer-associated retinopathy (CAR syndrome) with antibodies reacting with retinal, optic-nerve, and cancer cells. N Engl J Med 1989;321:1567-71.

99. Grunwald GB, Kornguth SE, Towfighi J, Sassani J, Simmonds MA, Housman CM, et al. Autoimmune basis for visual paraneoplastic syndrome in patients with small cell lung carcinoma: retinal immune deposits and ablation of retinal ganglion cells. Cancer 1987;60:780-6.

100. Erlandson RA, editor. Diagnostic transmission electron microscopy of human tumors. New York: Masson Publishing; 1981.

101. Ghadially FN, editor. Ultrastructural pathology of the cell matrix. London: Butterworth; 1982.

102. Geiger B, Schmid E, Franke WW. Spatial distribution of proteins specific for desmosomes and adherens junctions in epithelial cells demonstrated by double immunofluorescence microscopy. Differentiation 1983;23:189-205.

103. Miettinen M. Keratin subsets in spindle cell sarcomas: keratins are widespread but synovial sarcoma contains a distinctive keratin polypeptide pattern and desmoplakin. Am J Pathol 1991;138:505-13.

104. Kirsner RS, Anhalt GJ, Kerdel FA. Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. Br J Dermatol 1995;132:474-8.

105. Yee C, Biondi A, Wang XH, Iscove NN, de Sousa J, Aarden LA, et al. A possible autocrine role for interleukin-6 in two lymphoma cell lines. Blood 1989;74:798-804.

106. Emilie D, Devergne O, Raphael M, Coumbaras LJ, Galanaud P. Production of interleukin-6 in high grade B lymphomas. Curr Top Microbiol Immunol 1992;182:349-55.

107. Biondi A, Rossi V, Bassan R, Barbui T, Bettoni S, Sironi M, et al. Constitutive expression of the interleukin-6 gene in chronic lymphocytic leukemia. Blood 1989;73:1279-84.

108. Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, et al. Epitope spreading: lessons from autoimmune skin diseases. J Invest Dermatol 1998;110:103-9.

109. Huilgol SC, Black MM. Management of the immunobullous disorders. II. Pemphigus. Clin Exp Dermatol 1995;20:283-93.

110. Stendahl O, Molin L, Dahlgren C. The inhibition of polymorphonuclear leukocyte cytotoxicity by dapsone: a possible mechanism in the treatment of dermatitis herpetiformis. J Clin Invest 1978;62:214-22.

111. Piette W, Burken RR, Ray TL. Intraepidermal neutrophilic IgA dermatosis: presence of circulating pemphigus-like IgA antibody specific for monkey epithelium [abstract]. J Invest Dermatol 1987;88:512.

112. Burrows D, Bingham EA. Subcorneal pustular dermatosis and IgA gammopathy. Br J Dermatol 1984;111:91-3.

113. Norris DA, Osborn R, Robinson W, Tonnesen MG. Isotretinoin produces significant inhibition of monocyte and neutrophil chemotaxis in vivo in patients with cystic acne. J Invest Dermatol 1987;89:42-3.

114. Tankel M, Tannenbaum S, Parekh S. Paraneoplastic pemphigus presenting as an unusual bullous eruption. J Am Acad Dermatol 1993;29:825-8.

115. Su WPD, Oursler JR, Muller SA. Paraneoplastic pemphigus: a case with high titer of circulating anti–base-

ment membrane zone autoantibodies. J Am Acad Dermatol 1994;30:841-4.

116. Ryan JG. Pemphigus: a 20-year survey of experience with 70 cases. Arch Dermatol 1971;104:14-20.

117. Rosenberg FR, Sander S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. Arch Dermatol 1976;112:962-70.

118. Lever WF, White H. Treatment of pemphigus with corticosteroids: results obtained in 46 patients over a period of 11 years. Arch Dermatol 1963;87:12-26.

119. Truhan AP, Ahmed AR. Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. Ann Allergy 1989;62:375-91.

120. Ho VC, Zloty DM. Immunosuppressive agents in dermatology. Dermatol Clin 1993;11:73-85.

121. Rogers RS. Dapsone and sulfapyridine therapy of pemphigoid diseases. Australas J Dermatol 1986;27:58-63.

122. Stern RS. Systemic dapsone. Arch Dermatol 1993;129:301-3.

123. Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol 1993;129:507-13.

124. Huilgol SC, Black MM. Management of the immunobullous disorders. I. Pemphigoid. Clin Exp Dermatol 1995;20:189-201.

125. Guillot B, Donadio D, Guilhou JJ, Meynadier J. Long term plasma exchange therapy in bullous pemphigoid. Acta Derm Venereol (Stockh) 1986;66:73-5.

126. Bystryn JC. Plasmapheresis therapy of pemphigus. Arch Dermatol 1988;124:1702-4.