and their cultivation into epithelial sheets for grafting onto the patient’s skin. Results with a canine dystrophic epidermolysis bullosa model seem promising: transduction of epidermal cells with a retroviral vector containing the entire collagen VII cDNA enhanced expression and deposition of collagen VII at the dermal-epidermal junction.\(^\text{126}\)

In another approach, nonviral gene transfer using cotransfection of C31 integrase and human collagen VII resulted in the expression of the protein in collagen VII-deficient DBE keratinocytes.\(^\text{124}\) As fibroblasts also contribute to the synthesis of collagen VII, their suitability for gene therapy approaches is under investigation.\(^\text{128,129}\)

### Cellular Origin of the Dermal-Epidermal Basement Membrane

The basement membrane constituents are products of both epithelial and mesenchymal cells. In vitro modeling of basement membrane formation clearly shows that, under at least some conditions, the dermal-epidermal junction basement membrane is contributed to by both tissue compartments, and it has been proposed that differentiated fibroblasts exist adjacent to epithelial tissues in vivo, which produce basement membrane components and assist in basement membrane assembly.\(^\text{130,131}\) Of the known basement membrane components, only laminins 332 (laminin-5) and 511A (laminin-6) are exclusively produced by the epidermis. Epithelial cells also manufacture most of collagen VII, whereas mainly mesenchymal cells synthesize collagen IV, nidogen, perlecain, and the laminin \(\alpha2\) chain.\(^\text{131}\) Because the mesenchymal products are translocated to the basolateral epithelial surface where they condense, that surface must provide the localization cues. Integrins \(\alpha6\beta1\) and \(\alpha5\beta1\), and collagen XVII have been implicated in this process, suggesting that the laminins coordinate basement membrane polymerization.\(^\text{67,68,101}\)

As nidogen is required for stabilization of the basement membrane, and because it is a mesenchymal product, it is likely that the demis is essential to development of basement membranes.\(^\text{132}\) Studies using different skin equivalent culture models have demonstrated that a tight interplay between fibroblasts and keratinocytes, in terms of both their matrix production and secretion of soluble signals, regulates the formation of the dermal-epidermal basement membrane.\(^\text{132,134}\) An interesting regulatory step may be added by dermal enzymes (e.g., bone morphologic protein 1), which process epithelial cell products, such as laminin 332 and procollagen VII, to mature basement membrane molecules.\(^\text{103,104,114}\)

### Table 52-1

<table>
<thead>
<tr>
<th>Classification of Pemphigus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus IgA</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Fogo selvagem: Endemic Drug-induced</td>
</tr>
<tr>
<td>IgA pemphigus</td>
</tr>
</tbody>
</table>

**IgA = immunoglobulin A.**

with more localized disease, represented by pemphigus erythematosus. However, these patients often go on to more widespread PF.

### Key References

The full reference list for all chapters is available at www.digm7.com.


The discovery by Beutner and Jordon in 1964 of circulating antibodies against the cell surface of keratinocytes in the sera of patients with PV pioneered our understanding that PV is a tissue-specific autoimmune disease of skin and mucosa. Ultimately, their work led the way to the discoveries of autoantibodies and autoantigens.

**EPIDEMIOLOGY**

Several retrospective surveys of patients with PV, PF, or both clearly indicate that the epidemiology of pemphigus is dependent on both the area in the world that is studied as well as the ethnic population in that area.\(^{24-12}\) The prevalence of pemphigus of both types in men and women is nearly equal in most areas; however, notable exceptions are the predominance of women in an endemic focus of PF in Tunisia, and a predominance of men in an endemic focus of PF in Colombia.\(^{5,13}\) The mean age of onset of disease is approximately 40 to 60 years of age; however, the range is broad, and disease may start in the elderly and in children.

**Incidence and Prevalence**

**Pemphigus Vulgaris** PV is more common in Jews and probably in people of Mediterranean descent and from the Middle East. This same ethnic predominance does not exist for PF. Therefore, in areas where the Jewish, Middle Eastern, and Mediterranean population predominates, the ratio of PV to PF cases tends to be higher. For example, in New York, Los Angeles, and Croatia, the ratio of PV to PF cases is approximately 5:1; in Iran the ratio is 12:1; whereas in Finland, it is only 0.5:1.0, and in Singapore it is 2:1. Similarly, the incidence of pemphigus is variable depending on location: In Jerusalem, the incidence of PV has been estimated to be 1.6 per 100,000 population per year and in Iran approximately 10.0 per 100,000 per year; in Finland, the incidence is much lower, 0.76 per million population. In France and Germany, the incidence of PV is approximately 1.0 case per million population per year and that of PF is 0.5 cases per million per year. The prevalence and incidence of PF are also very dependent on its location, as best exemplified by fogo selvagem and other forms of endemic PF in Colombia and Tunisia.

**Fogo Selvagem** The first recognition of endemic PF was in Brazil and is called fogo selvagem, which means “wild fire” in Portuguese. It is a disease that is clinically, histologically, and immunopathologically the same as sporadic PF in any individual patient, but its epidemiology is unique.\(^{14,15}\) Fogo selvagem is endemic in the rural areas of Brazil, especially along inland riverbeds. The geographic distribution of disease clustering is similar to that of a black fly, *Simulium nigrimanum*, thought by natives to be a vector of this disease. A study of potential environmental risk factors has also implicated the bite of this black fly, showing it to be significantly more frequent among those with the disease compared to an age-, sex-, and occupation-matched control population with unrelated dermatoses.\(^{16}\) The prevalence on some well-studied Indian reservations in rural Brazil can be as high as 3.4 percent, with the incidence up to 0.8 to 4.0 new cases per 1000 people per year.\(^{15,17}\) On the reservation in Limao Verde, up to 55 percent of unaffected individuals have a low-level IgG1 antibody response against desmoglein 1, the PF autoantigen (see Pemphigus Antigens), which becomes an IgG4 response of higher titer against a more pathogenic epitope in disease.\(^{15}\) These results suggest that some environmental agent (e.g., insects or other infectious disease agent) may trigger a low-level autoantibody response that becomes more generalized by intramolecular epitope spreading in genetically susceptible individuals. With this theory in mind, it is interesting that 40 percent to 80 percent of patients from Brazil with the insectborne diseases onchocerciasis, leishmaniasis, and Chagas disease have low-level anti-desmoglein 1 antibodies, but patients with other infectious diseases from Brazil rarely have such antibodies.\(^{18}\)

Fogo selvagem occurs often in children and young adults, unlike sporadic PF, which is a disease of mostly middle-aged and older patients (although rare cases in children have been reported).\(^{19}\) Also unlike PF, fogo selvagem occurs not infrequently in genetically related family members, although it is not contagious. This fact probably implies a common exposure, as well as susceptibility. There is no known racial or ethnic predominance, and anyone moving into an endemic area may be susceptible to disease. Finally, the development of the rural endemic areas of Brazil decreased the incidence of disease. Certainly, this fascinating disease holds clues to understanding how this autoimmune response is triggered.

**ETIOLOGY AND PATHOGENESIS**

**Electron Microscopy**

Ultrastructural studies of the blisters in pemphigus have focused on the appearance of desmosomes, because these are the most prominent cell-to-cell adhesion junctions in stratified squamous epithelia. Early studies of PV lesions seemed to demonstrate early dissolution of cell-to-cell membrane contacts between intact desmosome junctions, with later separation and disappearance of the desmo-
somes. In acantholytic cells, separation of the opposing desmosomal plaques was seen, leaving half-desmosomes with the tonofilaments still inserted into the plaque. Such observations of acantholysis with half-desmosomes without tonofilament collapse have also been reported in a mouse model of PV. In contrast, the addition of PV serum to cultured keratinocytes affects desmosome structure by causing the retraction of the tonofilaments that normally attach to desmosomal plaques. Biopsies of uninvolved skin from patients with PV show disruption of desmosomes and decreased numbers of desmosomes. All these data confirm that at various time points during acantholysis, the desmosome is affected and ultimately destroyed, consistent with the cell biologic data discussed in Pathophysiology of Acantholysis.

Similarly, in lesions of PF, electron microscopy was reported to show abnormalities in desmosome structure in early acantholysis and in the mucosa, which binds autoantibodies but does not undergo gross acantholysis. The earliest of these changes may be retraction of tonofilaments from the desmosome-dense plaque. Later, there may be a decrease or absence of desmosomes. These electron microscopic studies are difficult to interpret regarding the time course of events, but they all indicate that, at least in some stage of acantholysis, desmosomes are destroyed.

**Immunopathology**

**IMMUNOFLUORESCENCE** The hallmark of pemphigus is the finding of IgG autoantibodies against the cell surface of keratinocytes. These autoantibodies were first discovered in patients’ sera by indirect immunofluorescence and soon thereafter were discovered by direct immunofluorescence of patients’ skin. Essential all patients with active PV or PF have a positive finding on a direct immunofluorescence test for IgG on the cell surface of keratinocytes in perilesional skin (Fig. 52-1A). The diagnosis of pemphigus should be seriously questioned if the test result of direct immunofluorescence is negative. Depending on the substrate used for indirect immunofluorescence, more than 80 percent of patients with pemphigus have circulating antiparietal cell surface IgG (Fig. 52-1B). Patients with early localized disease and those in remission are most likely to have negative findings on an indirect immunofluorescence test.

Patients with PV and those with PF usually display similar direct and indirect immunofluorescence findings with IgG on the cell surface of epidermal cells throughout the epidermis. Therefore, it is usually not possible to differentiate the two diseases by the pattern of immunofluorescence. The substrate used to detect pemphigus antibody binding in indirect immunofluorescence greatly influences the sensitivity of the test, however. In general, monkey esophagus is more sensitive for detecting PV antibodies and guinea pig esophagus is a superior substrate for detecting PF antibodies.

There is a positive, but imperfect, correlation between the titer of circulating anti–cell surface antibody and the disease activity in PV and in PF. Although this correlation may hold in general, and although patients in remission often show serologic remission with negative direct and indirect immunofluorescence findings, disease activity in individual patients does not necessarily correlate with antibody titer. Therefore, in the day-to-day management of these patients, following disease activity is much more important than following antibody titer.

Pemphigus erythematosus is a localized form of PF with a characteristic direct immunofluorescence finding of immunoreactants, usually IgG and C3, at the basement membrane zone of erythematous facial skin. These immunoreactants are in addition to the epidermal cell surface IgG.

**Pemphigus Antigens** Immunologic evidence and molecular cloning have demonstrated that pemphigus antigens are desmogleins, transmembrane glycoproteins of desmosomes (cell-to-cell adhesion structures). Immunoelectron microscopy has localized both PV and PF antigens to the cell surface of keratinocytes in desmosomal junctions.

Characterization of pemphigus antigens at a molecular level has confirmed that they are molecules in desmosomes. Immunoprecipitation and immunoblotting studies with extracts from cultured keratinocytes or epidermis have demonstrated that PF antigen (as well as the fogo selvagem antigen) is desmoglein 1, a 160-kd transmembrane glycoprotein of desmosomes.

Molecular cloning of the complementary DNA that encodes PV antigen identified it as desmoglein 3, another desmoglein isoform encoded by a separate gene. All patients with PV have anti–desmoglein 3 antibodies, and some of these patients also have anti–desmoglein 1 antibodies. Patients with PV that affects predominantly mucous membranes tend to have only anti–desmoglein 3 antibodies, whereas those with mucocutaneous disease usually have both anti–desmoglein 3 and anti–desmoglein 1 antibodies. The dual antibody status of some patients with PV is in contrast to the single antibody status of PF patients, who have antibodies against only desmoglein 1.

Desmogleins 1 and 3 are closely related members of the cadherin supergene family. The original members of this family (e.g., E-cadherin) have been shown to be transmembrane, calcium-dependent, homophilic cell adhesion molecules. Presumably, the desmogleins fulfill similar functions in desmosomes. PF and PV sera bind calcium-sensitive, conformational epitopes on desmogleins 1 and 3, respectively, suggesting that they might interfere with a calcium-sensitive adhesion function.

Although other cell surface molecules, such as acetylcholine receptors, may modulate adhesion, their direct involvement in the pathophysiology of pemphigus is controversial.

**ENZYME-LINKED IMMUNOSORBENT ASSAY FOR IMMUNODIAGNOSIS** For diagnosis of disease, antigen-specific enzyme-linked
immunosorbent assays have been shown to be more sensitive and specific (e.g., they can differentiate PV from PF) than immunofluorescence, and their ti-
ter correlates better than that of indirect
immunofluorescence with disease activity.55,56 These assays use desmogleins 1 and 3 bound to plates, which are then incubated with patient sera and de-
veloped with anti-human IgG reagents. Such assays can differentiate between PV and foliaceous.43,49,53,54 In most cases, enzyme-linked immunosorbent assay is
positive for desmoglein 3 (but not des-
moglein 1) in mucosal PF, is positive for
both desmogleins 3 and 1 in PV with both mucosal and significant skin in-
volveinent, and is positive for only des-
moglein 1 in PF.

Pathophysiology of Acantholysis (See Chap. 51)

Pemphigus autoantibodies both from pa-
tients with PV and from those with PF are
pathogenic. The occurrence of neonatal PV demonstrates that maternal IgG can
cross the placenta and cause disease.55 However, neonatal PF is very rare.56

Essentially, neonatal PV results from
the passive transfer of IgG to the fetus. Similar experimental passive transfer
studies show that PV and PF IgG cause
acantholysis at the suprabasilar and gran-
ular layers of the epidermis, respectively, when added to skin in organ culture.57,58
Antibody-induced acantholysis in this
system occurs without the participation of complement or inflammatory cells.

Further compelling evidence of auto-
antibody-mediated pathology in pem-
phigus comes from studies of the pas-
sive transfer of PV and PF IgG to
neonatal mice. These mice develop blis-
ters and erosions that clinically and his-
tologismic correspond to those seen in PF, for
instance the anti–desmoglein 1 antibod-
yes bind throughout the epidermis and
mucous membranes, yet blisters occur
only in the superficial epithelium. This
parent paradox has been explained by
an antibody-mediated pathway in pemphigus.59,60 Complement
fixation is not necessary to produce dis-
ease, and, consistent with this observa-
tion, when monovalent Fab’ immunoglo-
bulin fragments are pathogenic in these
mice.59,61

The pathology-causing autoantibod-
ies in pemphigus are those directed against desmogleins 1 and 3.35,36 IgG
that is affinity purified from PV sera on
the extracellular domain of desmoglein
3 can cause suprabasilar acantholysis,
the typical histologic finding of PV le-
sions, when injected into neonatal
mice.62,63 Furthermore, the extracellular
domain of desmoglein 3 can adsorb out
of PV sera antibodies pathogenic in neo-
natal mice.64 Similarly, the extracellular
domain of desmoglein 1 can adsorb out
all pathogenic antibodies from PF sera, and antibodies affinity purified on des-
moglein 1 are pathogenic.65 Finally, an
active animal model of PV has been es-
blished by immunizing mice that are
not tolerant of desmoglein 3 (i.e., mice
whose desmoglein 3 gene has been de-
leted) to generate an immune response
against desmoglein 3.58 After the pas-
sive transfer of lymphocytes from these
immunized mice to normal mice, the
latter develop clinically and histologi-
cally typical lesions of PV and have anti–desmoglein 3 antibodies in their
skin and sera.

These data strongly suggest that PV
and PF autoantibodies against desmo-
gleins 3 and 1, respectively, cause the
blister formation in these diseases. They
may do so by interfering with a cell-to-
cell adhesion function of these desmo-
gleins or with their role in desmosome
assembly. If indeed the pathophysiol-
ogy of pemphigus arises from such anti-
bodies directly inhibiting the function of
desmoglein, interfering with the func-
tion of the desmoglein in some other
way should result in a process that
mimics pemphigus. This hypothesis
was tested by genetically engineering a
mouse with a targeted deletion of the
desmoglein 3 gene.66,67 The phenotype of
this knockout mouse was very similar
to that of patients with PV, with supra-
basilar blisters developing in the oral
mucosa and skin. These data, then, are
consistent with the idea that autoanti-
bodies directly cause a loss of adhesion
of keratinocytes.

Another line of evidence that inacti-
vation of desmogleins causes the blister-
ing of pemphigus comes from studies of
bullaous impetigo and staphylococcal
scalded-skin syndrome, which are caused
by exfoliative toxin released by Sta-
phylococcus aureus. Desmoglein 1 is the
specific target for exfoliative toxin.
The enzyme proteolytically cleaves des-
monoglegin 1, resulting in blisters identical
to those seen in PF.68 Thus, inactivation
of desmoglein 1 can cause blisters iden-
tical to those seen in PF, which suggests
that the anti–desmoglein 1 antibodies in
PF patients also inactivate desmoglein 1.
Finally, in a mouse model of PV, anti-
desmoglein 3 antibodies appear to di-
terface with desmoglein function
within the desmosome, causing split desmosomes, without keratin re-
traction, in areas of acantholysis.22

If inactivation of desmoglein isoforms
results in blistering, then why do blisters
in PV and PF have specific tissue localiza-
tions that do not necessarily correlate
with the sites at which the antibodies
bind by immunofluorescence? In PV, for
example, the anti–desmoglein 1 antibod-
ies bind throughout the epidermis and
mucous membranes, yet blisters occur
only in the superficial epithelium. This
parent paradox has been explained by
desmoglein compensation, as outlined in
Fig. 52-2. The concept of desmoglein
compensation originates in the assump-
tion that autoantibodies against one des-
moglein isofom inactivate only that
isofom and that another isofom co-
expressed in the same area can compen-
sate in adhesion.70,71 Desmoglein com-
pensation also explains why neonatal
PF is so unusual, even though the anti–
desmoglein 1 antibodies cross the pla-
centa; in neonatal skin, as opposed to
adult skin, desmoglein 3 is co-expressed
with desmoglein 1 in the superficial epi-
dermis.72 The validity of desmoglein
compensation has been proven by the demon-
stration that transgenic mice with forced
expression of desmoglein 3 in the superfi-
cial epidermis are protected against blister-
ing by passive transfer of PF IgG.72 Further evidence for desmoglein compensation has been obtained on the genetic level.73

Specifically, transgenic expression of
desmoglein 1 can compensate for genetic loss of desmoglein 3 in knockout mice.

Recently it has been shown that an-
other desmoglein, desmoglein 4, which
is in the developing hair cortex and is
mutated in some types of autosomal re-
cessive hypotrichosis, is also present in
the superficial epidermis, and is a target
of some pemphigus antibodies.74-77

However, the anti–desmoglein 4 antibod-
ies in mucocutaneous PV and in PF also
bind desmoglein 1 and do not seem to be
sufficient or necessary for acantholysis.78

Although the anti–desmoglein antibod-
ies in pemphigus may directly inactivate
desmogleins in desmosomes, thereby
causing loss of cell adhesion, it is also
possible that they deplete the desmo-
some of desmoglein.79-82 This effect
may occur by depletion of desmoglein from
the cell surface before it becomes in-
corporated into the desmosome, thus
decreasing the precursor pool. Another pos-
sibility is that pemphigus antibodies
might cause depletion of desmoglein di-
rectly from the desmosomes. In either
case, PV antibodies have been shown to
bind desmoglein 3 (together with plako-
globin) for endocytosis and lysosomal
degradation. It has been shown that ad-
hesion on the cell surface is necessary to
prevent endocytosis of organizing des-
mosomes,65 therefore desmoglein inter-

462
nalization and degradation may reflect the pemphigus antibody-induced loss of adhesion function. However, depletion, acantholysis, or both may also be dependent on antibody-mediated intracellular signaling that may or may not depend on loss of adhesion. Various observations have implicated signaling, which may simply be associated with acantholysis or may be causal. Some examples follow: PV added to keratinocytes causes phosphorylation of desmoglein 1, which in turn is associated with its dissociation from plakoglobin. Plakoglobin itself, which may be part of some signaling pathways, is necessary in culture for PV IgG to cause retraction of keratin filaments, which may be a marker for early acantholysis. Phosphorylation of heat shock protein 27 in cells treated with PV IgG has implicated the p38MAPK signaling pathway, and inhibition of this pathway prevents cytoskeletal reorganization, presumably associated with loss of cell adhesion, in these cells. Finally, blocking various signaling pathways prevents acantholysis caused by PV IgG in neonatal mice. Which, if any, of these signaling mechanisms is necessary or sufficient for acantholysis, their exact involvement in causing acantholysis or whether they are activated as a result of acantholysis, remains to be determined.

Genetic Restriction of the Pemphigus Immune Response

Compared to a matched population, patients with PV have a markedly increased frequency of certain class II major histocompatibility complex (MHC) antigens. Among Ashkenazi Jews with PV, the serologically defined HLA-DR4 haplotype is predominant, whereas in other ethnic groups with PV, the DQ1 allele is more common. However, the association with disease susceptibility becomes even more striking in an analysis of these MHC alleles at a genetic level to determine the amino acid sequence of the cell surface molecules that they encode. Patients with the DR4 serotype almost all have an unusual allele called DRB1*0402, and patients with the DQ1 serotype almost all have a rare allele called DQB1*0503. The protein chains encoded by these alleles vary from those encoded by the alleles found in HLA-DR4 and DQ1 controls without disease in only a few amino acids.

These MHC alleles encode cell surface molecules that are necessary for antigen presentation to the immune system; therefore, it is hypothesized that the disease-associated MHC class II antigens allow presentation of desmoglein 3 peptides to T cells. Consistent with this hypothesis is the finding that certain peptides from desmoglein 3, predicted to
Pemphigus Vulgaris

SKIN The skin lesions in PV are rarely pruritic, but are often painful.1 The primary lesion of PV is a flaccid blister, which may occur anywhere on the skin surface (Fig. 52-3). Usually, the blister arises on normal-appearing skin, but it may develop on erythematous skin. Even new blisters are usually flaccid or become so within a short time. Because these blisters are fragile, intact blisters may be sparse. The most common skin lesions that occur in these patients are erosions, often painful, subsequent to broken blisters. These erosions are often quite large, as they have a tendency to spread at their periphery (Fig. 52-4). This characteristic finding can be elicited in pemphigus patients with active blistering by applying lateral pressure to normal-appearing skin at the periphery of active lesions. The result is a shearing away of the epidermis in normal-appearing areas, a phenomenon known as the Nikolsky sign.100 This sign helps differentiate pemphigus from other blistering diseases of the skin (Box 52-1).

In certain patients, erosions have a tendency to develop excessive granulation tissue and crusting (Fig. 52-5); that is, these patients display more vegetating lesions. This type of lesion tends to occur more frequently in intertriginous areas, in the scalp, or on the face (see Fig. 52-5A). In pemphigus vegetans of Hallopeau, vegetating lesions are present from the outset of disease (see Fig. 52-5B). Before the advent of effective therapy for pemphigus, the prognosis for these patients was not as grave as that for patients with the more usual type of PV. In other patients (e.g., those with pemphigus vegetans of Neumann), ordinary PV erosions may tend to develop vegetations. The vegetating type of response may also appear in certain lesions that tend to be resistant to therapy and remain for long periods of time in one place. Thus, vegetating lesions seem to be one reactive pattern of the skin to the autoimmune insult of PV, with certain areas of the skin showing more of a tendency to form vegetations.

MUCOUS MEMBRANES In the majority of patients, painful mucous membrane erosions are the presenting sign of PV and may be the only sign for an average of 5 months before skin lesions develop (see Fig. 52-3B).4 However, the presenting symptoms may vary according to geographic area; for example in a study from Croatia, painful oral lesions were the presenting symptom in only 82 percent of patients. Most of these patients progressed to a more generalized eruption in 5 months to 1 year; however, some had oral lesions for more than 5 years before generalization.11 On the other hand, in Tehran, 62 percent of patients presented with oral lesions.9 The mucous membranes most often affected are those of the oral cavity, which is involved in almost all patients with PV and is often the only mucous membrane involved (see Fig. 52-3B). Intact blisters are rare, probably because they are fragile and break easily. Scattered and often extensive erosions may appear on any part of the oral cavity, although they perhaps occur most frequently on the buccal mucosa. These erosions may spread to involve the pharynx...
and larynx with subsequent hoarseness. Often, these erosions are so uncomfortable and, in fact, painful that the patient is unable to eat or drink adequately.

Mucous membranes in other areas may also be involved with painful erosions; these include nasal mucosa, conjunctiva, anus, penis, vagina, and labia. Even the esophagus has been reported to be involved in unusual cases. Skin involvement without mucous membrane involvement in PV is unusual and accounts in one study for only 11 percent of cases.

Pemphigus Foliaceus

**SKIN** The characteristic clinical lesions of PF are scaly, crusted erosions, often on an erythematous base. In more localized and early disease, these lesions are usually well demarcated and scattered in a seborrheic distribution, including the face, scalp, and upper trunk. The primary lesions of small flaccid blisters are often inconspicuous and difficult to find. Disease may stay localized for years, or it may rapidly progress to sometimes generalized involvement, resulting in an exfoliative erythroderma. Exposure to sun, heat, or both may exacerbate disease activity. Patients with PF often complain of pain and burning in the skin lesions. In contrast to patients with PV, those with PF only very rarely, if ever, have mucous membrane involvement, even with widespread disease.

The colloquial term for Brazilian endemic pemphigus, fogo selvagem (Portuguese for “wild fire”), takes into account many of the clinical aspects of this disease: the burning feeling of the skin, the exacerbation of disease by the sun, and the crusted lesions that make the patients appear as if they had been burned.

Pemphigus Erythematosus

Also known as Senear-Usher syndrome, pemphigus erythematosus is simply the localized form of PF. Typical scaly and crusted lesions of PF occur across the malar area of the face and in other seborrheic areas. Pemphigus erythematosus may remain localized for years, or it may evolve into more generalized PF. If there is a unique aspect of pemphigus erythematosus, it is the immunofluorescence findings noted in Immunopathology.

In addition, many patients with pemphigus erythematosus show serologic findings suggestive of systemic lupus erythematosus, especially the presence of anti-nuclear antibodies, although few patients have been reported to actually have the two diseases concurrently.

**Neonatal Pemphigus**

Infants born to mothers with PV may display clinical, histologic, and immunopathologic signs of pemphigus. The degree of involvement varies from none to severe enough to result in a stillbirth. If the infant survives, disease tends to remit as maternal antibody is catabolized. Mothers with PF may also transmit their autoantibodies to the fetus, but, as discussed in Pathophysiology of Acantholysis, neonatal PF occurs only rarely. Neonatal pemphigus should be distinguished from PV and PF that occur in childhood, which are similar to the autoimmune diseases seen in adults.

**Drug-Induced Pemphigus**

Although there are sporadic case reports of pemphigus associated with the use of several different drugs, the association with penicillamine, and perhaps captopril, is the most significant. The prevalence of pemphigus in penicillamine users is estimated to be approximately 7 percent. PF (including pemphigus erythematosus) is more common than PV in these penicillamine-treated patients, although either may occur. The findings of direct and indirect immunofluorescence are positive in most of these patients. Three patients with drug-induced PF and one with drug-induced PV have been shown to have autoantibodies to the same molecules involved in sporadic pemphigus, namely, desmoglein 1 and desmoglein 3, respectively. Therefore, by immunofluorescence and immu-
Both penicillamine and captopril contain sulphydryl groups that may interact with the sulphydryl groups in desmoglein 1, 3, or both, thereby causing pemphigus either by directly interfering with these adhesion molecules or, more likely, by modifying them so that they become more antigenic. The use of these drugs may also lead to a more generalized dysregulation of the immune response, allowing production of other autoantibodies such as those resulting in myasthenia gravis. Most, but not all, patients with drug-induced pemphigus go into remission after they stop taking the offending drug.

Associated Diseases

Myasthenia gravis, thymoma, or both have been associated with PV and PF.\textsuperscript{114} Approximately one-half of associated pemphigus cases are vulgaris; one-half, foliaceus or erythematosus. Most of these data, however, were reported before the recognition of paraneoplastic pemphigus as a distinct entity. Therefore, although thymoma may clearly be associated with PV and PF, it may also be associated with paraneoplastic pemphigus (see Chap. 53). The course of myasthenia gravis and the course of pemphigus seem independent of each other. Likewise, the thymic abnormality may either precede or follow the onset of pemphigus. Thymic abnormalities include benign or malignant thymoma and thymic hyperplasia. Irradiation of the thymus or thymectomy, although clearly beneficial for myasthenia gravis, may not improve the pemphigus disease activity. Although this association is reported in at least 30 cases, the finding of thymoma or myasthenia gravis in a patient with PV or PF is still unusual.

Although very uncommon, PV or PF has been associated with bullous pemphigoid in the same patient.\textsuperscript{115} Finally, PV has rarely evolved into PF, and vice versa, as determined by clinical, histologic, and immunohistochemical criteria.\textsuperscript{116–118} Approximately one-half of associated pemphigus cases are vulgaris; one-half, foliaceus or erythematosus. Most of these data, however, were reported before the recognition of paraneoplastic pemphigus as a distinct entity. Therefore, although thymoma may clearly be associated with PV and PF, it may also be associated with paraneoplastic pemphigus (see Chap. 53). The course of myasthenia gravis and the course of pemphigus seem independent of each other. Likewise, the thymic abnormality may either precede or follow the onset of pemphigus. Thymic abnormalities include benign or malignant thymoma and thymic hyperplasia. Irradiation of the thymus or thymectomy, although clearly beneficial for myasthenia gravis, may not improve the pemphigus disease activity. Although this association is reported in at least 30 cases, the finding of thymoma or myasthenia gravis in a patient with PV or PF is still unusual.

Pemphigus Foliaceus

The characteristic histopathologic finding in PV is a suprabasilar blister with acantholysis (Fig. 52-7). Just above the basal cell layer, epidermal cells lose their normal cell-to-cell contacts and form a blister. Often, a few rounded up (acantholytic) keratinocytes are in the blister cavity. The basal cells stay attached to the basement membrane, but may lose the contact with their neighbors; as a result, they may appear to be a “row of tombstones.” Usually, the upper epidermis (from one or two cell layers above the basal cells) remains intact, as these cells maintain their cell adhesion. Pemphigus vegetans shows not only suprabasilar acantholysis, but also papillomatosis of the dermal papillae and downward growth of epidermal stands into the dermis, with hyperkeratosis and scale-crust formation. In addition, pemphigus vegetans lesions may show intraepidermal abscesses composed of eosinophils.\textsuperscript{119} Early PV lesions may show eosinophilic spongiosis.\textsuperscript{119}

Pemphigus Vulgaris

One early histopathologic finding in PV is a suprabasilar blister with acantholysis (Fig. 52-7). Just above the basal cell layer, epidermal cells lose their normal cell-to-cell contacts and form a blister. Often, a few rounded up (acantholytic) keratinocytes are in the blister cavity. The basal cells stay attached to the basement membrane, but may lose the contact with their neighbors; as a result, they may appear to be a “row of tombstones.” Usually, the upper epidermis (from one or two cell layers above the basal cells) remains intact, as these cells maintain their cell adhesion. Pemphigus vegetans shows not only suprabasilar acantholysis, but also papillomatosis of the dermal papillae and downward growth of epidermal stands into the dermis, with hyperkeratosis and scale-crust formation. In addition, pemphigus vegetans lesions may show intraepidermal abscesses composed of eosinophils.\textsuperscript{119} Early PV lesions may show eosinophilic spongiosis.\textsuperscript{119}

PROGNOSIS AND CLINICAL COURSE

Before the advent of glucocorticoid therapy, PV was almost invariably fatal, and PF was fatal in approximately 60 percent of patients. PF was almost always fatal in elderly patients with concurrent medical problems; however, in other patients its prognosis, without therapy, was much better than PV.\textsuperscript{120,121} The systemic administration of glucocorticoids and the use of immunosuppressive therapy have dramatically improved the prognosis for patients with pemphigus; however, pemphigus is still a disease associated with a significant morbidity and mortality.\textsuperscript{122,123} Infection is often the cause of death, and by causing the immunosuppression necessary in the treatment of active disease, therapy is frequently a contributing factor.\textsuperscript{124} With glucocorticoid and immunosuppressive therapy, the mortality (from disease or therapy) of PV patients followed from 4 to 10 years is ap-
proximately 10 percent or less, whereas that of PF is probably even less. In a more recent study of 40 patients with PV, 2 patients (5 percent) died of sepsis and 17 percent, after an average of 18 months of therapy, went into a complete and long-lasting (>4 years, average, thought to be permanent) remission requiring no further therapy.125 Another 37 percent of patients achieved remission but relapsed at times after therapy was stopped; most of these also eventually achieved long-lasting remissions. The remainder of patients required continual therapy. In a group of 159 patients with PV from Croatia, only approximately 12 percent went into long-term remission after therapy with glucocorticoids and immunosuppressives, but most relapsed.11 In a study from Tehran of 1206 pemphigus patients seen over 20 years, 6.2 percent of PV and 0.2 percent of PF patients died; mostly of septicemia; only 9.5 percent were in complete remission without therapy.9

**TREATMENT**

Approach to therapy of pemphigus varies widely, even among experts.126 It is generally agreed that PV, even if initially limited in extent, should be treated at its onset, because it will ultimately generalize and the prognosis without therapy is very poor. In addition, it is probably easier to control early disease than widespread disease, and mortality may be higher if therapy is delayed.127

Because PF may be localized for many years, and the prognosis without systemic therapy may be good, patients with this type of pemphigus do not necessarily require treatment with systemic therapy; the use of topical glucocorticoids may suffice. When the disease is active and widespread, however, the therapy for PF is, in general, similar to that for PV.

The systemic administration of glucocorticoids, usually prednisone, is the mainstay of therapy for pemphigus. At one time, primarily before available immunosuppressive therapy was available, very high initial doses of prednisone were recommended for therapy. Now, however, few authorities recommend such high doses, and many feel that intermediate or low doses, especially if used in combination with immunosuppressive therapy and, if necessary, with tolerance of some residual disease activity, result in fewer complications and decreased mortality.7,124,129,129 However, some experts in pemphigus still recommend controlling active disease initially with escalating doses of prednisone.121,129 Once disease activity is controlled, tapering prednisone to as low a dose as possible should be the goal.

Interestingly, prednisone can control blistering in as few as several days, at a time when the autoantibody titer would be unchanged. How, then, could it work to control disease? One possibility is that it may increase the synthesis of desmogleins or change their post-transcriptional modification to prolong their half-life.121 If, as discussed in *Pathophysiology of Acantholysis*, pemphigus IgG depletes desmosomes of desmogleins, then prednisone could counteract this effect.

Although there are few controlled studies, most authors feel that immunosuppressive agents, such as mycophenolate mofetil (CellCept), azathioprine (Imuran), and cyclophosphamide (Cytoxan), have a steroid-sparing effect, decrease the incidence of side effects of therapy, and may increase the numbers of remissions.32,120,122,127,128 Usually, mycophenolate mofetil or azathioprine, which has less potential adverse effects than cyclophosphamide, is the initial immunosuppressive agent.133,134 Treatment regimens often begin with both an immunosuppressive agent and prednisone in moderate to intermediate doses, depending on disease activity, although some authors suggest first determining if the disease responds to a course of glucocorticoids alone.32,123,129 In any case, if there are contraindications to glucocorticoid use, if the glucocorticoids do not control the disease, or if a dosage low enough to minimize the risk of steroid complications is not effective, the patient should receive adjuvant therapy, usually consisting of immunosuppressive agents.

Results obtained by using prednisone and immunosuppressive agents to treat patients with PV, although not controlled, have been impressive. For example, in a series of 29 patients treated with prednisone and azathioprine, approximately 50 percent went into clinical and serologic remission and continued off therapy for a mean follow-up of 4 years.32 Many of these patients were considered cured. Only one patient in this study died because of complications of therapy. The disease activity of most of the other patients was well controlled.

Mycophenolate mofetil has been shown to have a rapid effect in lowering pemphigus antibody titers and to decrease disease activity, even in patients whose disease is unresponsive to azathioprine.132–134 As it probably has fewer adverse reactions than azathioprine, it has, in some centers, replaced azathioprine as a first-line agent in treating these patients.

Cyclophosphamide, although more toxic than azathioprine or mycophenolate mofetil, is thought to be very effective in controlling severe disease, with one report of 19 of 23 patients with pemphigus achieving complete remission in a median time of 8.5 months.133 Early localized PV may be treated with relatively low-dose prednisone (e.g., 20 mg), often with an immunosuppressive agent.136 The decision to use immunosuppressive agents in young patients must take into account the potential increased incidence of malignancies that might be associated with the use of these drugs, as well as the risks of infertility (especially associated with cyclophosphamide) and teratogenicity. In some patients, especially those who are elderly with limited disease or those in whom glucocorticoids are contraindicated, immunosuppressive agents alone may be used.137 Because patients may die from complications of therapy, it is important to monitor all patients closely for potential side effects, such as infection, diabetes, leukopenia, thrombocytopenia, anemia, gastrointestinal ulcer disease, bleeding, liver and renal function abnormalities, high blood pressure, electrolyte disturbances, and osteoporosis.

There are additional, innovative therapies that are usually used when more standard treatment is not effective. For example, the intravenous, pulse administration of methylprednisolone, 250 to 1000 mg given over approximately 3 hours q24h for 4 to 5 consecutive days, can result in long-term remissions and decrease the total dose of glucocorticoids necessary to control disease.138 Although the purpose of this therapy is to decrease the incidence of complications
cells that provide “help” in stimulating the autoantibody response. Rituximab is given as intravenous therapy once a week for 4 weeks, and such a course can be repeated in approximately 6 months. Improvement is usually seen within 1 to 2 months after the course of therapy. Most patients show at least partial remission and some show dramatic complete remissions; however, serious infections and other adverse effects may be seen, some of which may be due to concomitant use of other immunosuppressives.

Plasmapheresis is sometimes used, in combination with cyclophosphamide or another immunosuppressive agent, for severe pemphigus, or for pemphigus which is unresponsive to a combination of prednisone and immunosuppressive agents. Although one controlled study found it to be ineffective, other studies have found that it both reduces serum levels of pemphigus autoantibodies and controls disease activity. For maximum effectiveness, it is probably necessary to perform plasmapheresis on patients taking immunosuppressive agents to prevent the antibody-rebound phenomenon that can follow the removal of IgG.

Other potential therapies for pemphigus, used less frequently than those that have been discussed, include immunoblastic therapy without stem cell rescue; the administration of cyclosporine, gold, antimalarials, or dapsone; and extracorporeal photochemotherapy. All in all, there has been a tremendous advance in the armamentarium of therapies for pemphigus since the time before the development of glucocorticoids. These advances, as well as cardiac arrhythmias with sudden death, and its use is controversial. Furthermore, a controlled trial found that adjunct oral dexamethasone pulse therapy in addition to standard therapy with prednisolone and azathioprine for PV is not beneficial. It may be that simply giving divided lower doses of prednisone could accomplish the same result with fewer side effects. Intravenous pulse therapy with cyclophosphamide, with or without pulse therapy with glucocorticoids, has also been reported to result in remissions of PV. The advantage of this therapy over that of daily cyclophosphamide has not been clearly established.

Another method of decreasing serum autoantibodies is the intravenous use of γ-globulin in high doses. It may be useful as an adjuvant therapy in those whose condition does not respond to more conventional therapy. It is thought to function by increasing catabolism of the patient’s antibodies, which include the pathogenic autoantibody. It seems to be effective for therapy but is expensive and requires many intravenous infusions for remission and continued infusions for maintenance of remission. There can also be significant side effects with this therapy.

Another potentially very effective therapy for pemphigus that is refractory to more standard therapy is a monoclonal anti-CD20 antibody (rituximab (Rituxan)), mostly used and approved for therapy of B-cell malignancies. In pemphigus patients, this monoclonal antibody would also presumably target B cells, the precursors of antibody-producing plasma cells. The B cell also acts to process autoantigen and present it to T cells that provide “help” in stimulating the autoantibody response. Rituximab is given as intravenous therapy once a week for 4 weeks, and such a course can be repeated in approximately 6 months. Improvement is usually seen within 1 to 2 months after the course of therapy. Most patients show at least partial remission and some show dramatic complete remissions; however, serious infections and other adverse effects may be seen, some of which may be due to concomitant use of other immunosuppressives.

Plasmapheresis is sometimes used, in combination with cyclophosphamide or another immunosuppressive agent, for severe pemphigus, or for pemphigus which is unresponsive to a combination of prednisone and immunosuppressive agents. Although one controlled study found it to be ineffective, other studies have found that it both reduces serum levels of pemphigus autoantibodies and controls disease activity. For maximum effectiveness, it is probably necessary to perform plasmapheresis on patients taking immunosuppressive agents to prevent the antibody-rebound phenomenon that can follow the removal of IgG.

Other potential therapies for pemphigus, used less frequently than those that have been discussed, include immunoblastic therapy without stem cell rescue; the administration of cyclosporine, gold, antimalarials, or dapsone; and extracorporeal photochemotherapy. All in all, there has been a tremendous advance in the armamentarium of therapies for pemphigus since the time before the development of glucocorticoids. These advances, as well as cardiac arrhythmias with sudden death, and its use is controversial. Furthermore, a controlled trial found that adjunct oral dexamethasone pulse therapy in addition to standard therapy with prednisolone and azathioprine for PV is not beneficial. It may be that simply giving divided lower doses of prednisone could accomplish the same result with fewer side effects. Intravenous pulse therapy with cyclophosphamide, with or without pulse therapy with glucocorticoids, has also been reported to result in remissions of PV. The advantage of this therapy over that of daily cyclophosphamide has not been clearly established.

Another method of decreasing serum autoantibodies is the intravenous use of γ-globulin in high doses. It may be useful as an adjuvant therapy in those whose condition does not respond to more conventional therapy. It is thought to function by increasing catabolism of the patient’s antibodies, which include the pathogenic autoantibody. It seems to be effective for therapy but is expensive and requires many intravenous infusions for remission and continued infusions for maintenance of remission. There can also be significant side effects with this therapy.

Another potentially very effective therapy for pemphigus that is refractory to more standard therapy is a monoclonal anti-CD20 antibody (rituximab (Rituxan)), mostly used and approved for therapy of B-cell malignancies. In pemphigus patients, this monoclonal antibody would also presumably target B cells, the precursors of antibody-producing plasma cells. The B cell also acts to process autoantigen and present it to T

Chap 53
Paraneoplastic Pemphigus
Grant J. Anhalt
Carlos H. Nousari

Paraneoplastic pemphigus (PNP) is an autoimmune disorder that is almost always linked to an underlying lymphoproliferative disorder. These features define it: (1) Painful stomatitis and a polymorphous cutaneous eruption with lesions that may be blistering, lichenoid, or resemble erythema multiforme. (2) Histologic findings that reflect the variability of the cutaneous lesions, showing acantholysis, lichenoid, or interface change. (3) Direct immunofluorescence demonstrating deposition of immunoglobulin G (IgG) and complement in the epidermal intercellular spaces, and often granular/linear complement deposition along the epidermal basement membrane zone. (4) Serum autoantibodies that bind the cell surface of skin and mucosae in a pattern typical for pemphigus, but in addition, bind to simple, columnar, and transitional epithelia. (5) These serum autoantibodies identify desmogleins 1 and 3, but additionally identify members of the plakin family of epithelial proteins, such as desmoplakins, envoplakin, and periplakin. The disease is associated, in the majority of cases, with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and Castleman disease. There is no regularly effective treatment and most patients die from complications of the disease, including pulmonary involvement with respiratory failure.