Abstract
Pemphigus and pemphigoid are the prototypical immunobullous diseases. Although it has been well established that they are caused by deposition of autoreactive antibodies directed against adherence proteins within the skin, the specific genetic and environmental factors leading to development of these diseases continue to be an area of investigation. Herein, we discuss several of the potential environmental triggers that may induce patients to develop immunobullous diseases including medications, viral infections, UV exposure or other radiation injury and dietary factors. In addition, the potential genetic and immunologic mechanisms contributing to the pathogenesis of pemphigus and pemphigoid will be reviewed. The multifactorial nature of these diseases contributes to their complexity and highlights the importance of a detailed personal and family history when caring for these patients.

Key Words: Autoimmune blistering diseases, desmoglein, pemphigoid, pemphigus

Introduction
Pemphigus and pemphigoid result from deposition of autoreactive antibodies directed against various intraepithelial and subepidermal proteins, resulting in the formation of bullae or erosions. Pemphigus is derived from the Greek word for blister, pemphix, and has several major variants: Pemphigus foliaceus, paraneoplastic pemphigus, pemphigus vegetans, pemphigus erythematosus, IgA pemphigus, drug-induced pemphigus, pemphigus fogo selvage and pemphigus vulgaris (PV). PV is the most common and well-characterized variant.

In pemphigoid, the dermal-epidermal junction is the autoimmune target resulting in a complete separation of the epidermis from the dermis. Bullous pemphigoid (BP) is the most common variant from the pemphigoid class of blistering diseases. Related diseases include cicatricial pemphigoid, linear IgA bullous dermatosis (LAD), epidermolysis bullosa acquisita (EBA), lichen-planus pemphigoides, and anti-p200 pemphigoid.

Although it has been well established that autoantibodies directed against adherence proteins within the skin is the underlying cause of all autoimmune bullous diseases, it is still unclear what factors lead to their occurrence. We plan to review the pathophysiology of the two most common autoimmune bullous diseases: PV and BP. Specifically, we will discuss the roles that genetic predisposition and environmental triggers play in the onset of these diseases.

Epidemiology, Presentation and Physical Exam
Incidence of pemphigus is estimated to be between 1 and 10 per million and individuals of Ashkenazi Jewish descent or of Mediterranean origin are at an increased risk. The peak incidence is between 30 and 60 years of age and the mean age of onset is between 50 and 60 years.

The prevalence in men and women is roughly equal.

In PV, autoantibodies are directed against desmoglein proteins within the epidermis, which leads to formation of bullae and erosions.
of characteristic flaccid blisters on the patient’s cutaneous and mucosal surfaces [Figure 1]. The hallmark physical exam findings are the direct and indirect Nikolskiy signs. A positive direct Nikolskiy sign is noted when digital pressure on intact skin results in sloughing off of the outermost layer. A positive indirect Nikolskiy sign (Asboe–Hansen sign) is when digital pressure to an intact bullous lesion leads to enlargement of the lesion to involve adjacent clear skin. In 66% of cases, disease onset occurs within the oral mucosa and disease may be limited to the oral cavity for months before progressing to the keratinized surfaces of the patient. Approximately 80% of patients with PV will have some oral involvement. In addition to skin and oral involvement, 50% of patients will have additional sites affected by PV including their nails, presenting as tender periungual erythema and edema; pharynx and larynx, resulting in dysphagia and hoarseness; and nasal cavity, presenting as nasal congestion with bloody mucus. In all cases, blisters may be associated with severe pain, pruritus, a burning sensation, or paresthesias. Prior to the discovery of an effective therapy, PV was fatal in approximately 70% of cases as a result of fluid/electrolyte-associated abnormalities and infection.

Pathophysiology

The pathogenesis of PV was established by Beutner and Jordon in 1964 when it was noted that pemphigus patients possessed autoantibodies to intercellular antigens found within the malphighian epithelia. Through in vitro studies on human skin and disease-associated IgG passive transfer experiments in mice, autoreactive IgG was identified as the reason for the acantholysis and bullae formation in PV. The most well-understood and accepted target antigens have been the calcium-dependent intercellular adhesion proteins that form the desmosomes, desmoglein (DSG) 1 and 3. The desmogleins are members of the cadherin protein family and are responsible for

Figure 1: Clinical photos of pemphigus lesions. (a) Flaccid bullae involving the scalp. (b) Erosions of oral cavity following blister rupture. (c) Characteristic flaccid blister with previously ruptured areas. (d and e) Widespread cutaneous erosions following rupture of bullae

Figure 2: Clinical photographs of pemphigoid lesions. (a) Ocular involvement by cicatricial pemphigoid with formation of symblepharon (adhesion between bulbar and palpebral conjunctivae). (b) Superficial erosions following rupture of cutaneous bullae. (c) Ruptured bullae on thumb and second digit, intact tense bullae on third digit. (d) Erosions following rupture of bullae. (e) Tense bullous lesion on medial thigh. (f) Bullous lesions in various stages, including intact as well as ruptured bullae and resulting erosions
anchoring keratin intermediate filaments to the cell membrane of epidermal cells. The type of desmoglein affected has clinical significance, as the location of PV lesions depends on the specific desmoglein targeted by the autoreactive immune response. DSG1 is most readily found within superficial layers of the epidermis. In contrast, DSG3 is more predominant within non-keratinized epithelia such as mucosal surfaces. The “compensation theory” established by Stanley and colleagues details how this distribution of target antigens leads to the different clinical presentations of PV. In areas where DSG 1 and DSG 3 are equally present, one desmoglein can compensate for the other’s loss of function. For example, a patient with auto-IgG4 to DSG1 will present with superficial cutaneous blisters because DSG3 is not present in sufficient quantities in the upper epidermis to compensate for the autoantibody-mediated functional loss of DSG1. These patients are unlikely to have mucosal involvement due to the compensatory action of DSG3 at those sites.

Although the role of DSG1 and 3 has been well established in pemphigus, the presence of other non-desmoglein antigens has also been suggested. For instance, anti-E-cadherin antibodies have been detected in PV patients at significantly higher levels than healthy controls. Keratinocyte acetylcholine receptors (AChRs) also play a role in cell–cell adhesion by regulating the intraepithelial expression of desmoglein and may act as potential non-desmoglein antigens. Supporting this theory is the association between PV and other autoimmune disorders involving AChRs including myasthenia gravis and thymoma-associated autoimmunity. Furthermore, in keratinocyte monolayers, addition of anti-α9 AChR IgG induced acantholysis that could be reversed with addition of the cholinergic agonist, carbachol.

The pemphigoid class of diseases is caused by autoantibodies against various components of hemidesmosomes, which are the cellular adhesion proteins linking individual basal keratinocytes to the underlying extracellular matrix of the epidermis. Specifically, autoreactive IgG1 and IgG4 antibodies target BP antigen 1 (BP230) and BP antigen 2 (BP180, also known as collagen XVII). BP180 is a type II transmembrane hemidesmosome protein, while BP230 is a cytoplasmic protein. Because BP230 is intercellular, there is some controversy regarding whether anti-BP230 IgG alone can cause BP. The majority of BP patients possess IgGs that specifically target the non-collagenous region, 16A (NC16A) of the BP180 ectodomain, and there is evidence that these patients also develop tissue resident memory B cells.

Although autoimmunity is the underlying cause of BP, it is still unknown how the loss of self-tolerance actually occurs. Some believe that autoimmunity results from a deficient interaction between Treg and autoreactive Th cells. In such a scenario, presentation of the BP180 and BP230 autoantigens by an MHC class II-expressing APC to self-reactive T cells will lead to T-cell activation, release of pro-inflammatory cytokines, up-regulation of co-stimulatory molecules on the surface of the APC, and activation of autoreactive BP180-specific B cells. Since characteristically BP involves recruitment of eosinophils and neutrophils, IL-17-secreting Th17 cells appear to be involved, which is similar to that seen in other inflammatory conditions such as psoriasis, systemic lupus erythematosus, and rheumatoid arthritis. Another hypothesized mechanism involves the binding of B-cell receptors and toll-like receptors (TLR) to self-antigens that possess an endogenous TLR ligand, resulting in B-cell activation and autoantibody secretion.

Recently, the existence of anti-BP180 IgE in BP patients has been reported, which is thought to synergize with autoreactive IgG1 and IgG4 to elicit complement activation, degranulation of mast cells, and release of leukotrienes, platelet-activating factor, TNF, and other cytokines. Recruited neutrophils and eosinophils also participate in the pathophysiology by releasing proteolytic enzymes which disrupt adhesion molecules, thereby contributing to the subepidermal blister formation. IgE involvement in BP is further supported by the finding that when a BP180 ectodomain (LABD97)-specific IgE-secreting hybridoma was injected into a SCID mouse, a basement membrane blistering disease developed that was histologically identical to BP.

**Genetic Predisposition**

The role of nature versus nurture is an ongoing debate in autoimmunity, as many diseases are multifactorial with both genetics and environment factors playing a role in their pathogenesis. The autoimmune blistering diseases PV and BP are no exception. Almost all patients with autoimmunity will first have a genetic predisposition for the disease such as disease-associated HLA gene or a mutation in a key regulatory protein of the immune system. But not all patients with a genetic predisposition will develop autoimmunity, suggesting that genetics alone is insufficient to cause autoimmunity. This argument has been supported by reports of PV occurring in only one monozygotic twin, and accounts of only two of three siblings with identical haplotypes developing disease.

PV has the strongest association with HLA class II genes, particularly DRα. Molecular gene subtyping showed the prevalence of either DRB1*0402 or DQB1*0503 in over 95% of patients. These two alleles are often associated with one another and their prevalence is increased in the Ashkenazi Jewish population. Other PV-associated DRB1 polymorphisms include DRB1*1401,
In the case of vaccines and interferons, after phenol exposure, γ even DQB1*0301 ACE inhibitors may promote acantholysis by inhibiting BP induced by thiols, it has been reported that phenols may induce autoimmune blistering diseases. After phenol exposure, keratinocytes release IL-1 and tumor necrosis factor (TNF), which may promote keratinocyte acantholysis.

Common phenol-containing medications associated with development of PV include aspirin, rifampicin, levodopa, heroin and some cephalosporins (which can also contain thiol groups). Aspirin can also induce BP via a mechanism similar to that of the thiol-based drugs. Specifically, it might bind to basement membrane proteins and act as a hapten to elicit an antigenic response. BP induced by TNF-blocking agents such as etanercept and adalimumab has also been reported but the exact mechanism for this effect remains unclear.

Various non-thiol or phenol-containing medications such as angiotensin-converting enzyme (ACE) inhibitors (other than captopril), vaccines, interferons, and nonsteroidal anti-inflammatory drugs (NSAIDs) have all been associated with the development of antibody-negative drug-induced PV. ACE inhibitors may promote acantholysis by inhibiting tissue transglutaminase, an enzyme involved in keratinocyte aggregation. In the case of vaccines and interferons, activation of the immune system is thought to result in autoimmune blister production and release of plasminogen activators by keratinocytes leading to acantholysis.

Viral infections, especially herpesvirus, cause inflammation that is marked by up-regulation of IFN-γ and the B-cell-supporting cytokines IL-4 and IL-10, along with other pro-inflammatory cytokines and antibodies, which have the potential to cause epithelial damage. In a study of 20 pemphigus patients, DNA sequencing identified the presence of herpes simplex virus, Epstein Barr virus, and human herpes virus-6 in the patient's lymphocytes and skin lesions. However, it is unclear if these viral infections are responsible for the induction of PV through a molecular mimicry mechanism or if their presence in the skin lesions is an incidental finding. Viral infections may likewise play a role in pemphigoid, particularly the herpesviruses. Although molecular mimicry is a conceivable mechanism linking infection with the onset of PV, the process of autoimmunity is often multifactorial, and as a result, such observations are difficult to interpret.

Traumatic injuries to the skin caused by excessive sun exposure or radiation therapy may lead to blister and bullae formation at the sites of injury due to localized exposure of self-antigens. The up-regulated local inflammatory response at sites of cutaneous injury may further contribute to an environment favoring autoantibody production. Radiation therapy has been noted to commonly cause BP in female breast cancer patients, by potentially modifying the basal membrane to expose BP antigens, resulting in antibody formation, complement activation, and a proinflammatory state.

Muramatsu and colleagues postulated that UVB exposure directly causes conformational changes in BP

Patients with pemphigoid tend to have an increased frequency of the allele DQB1*0301, and some studies have demonstrated that BP180-specific Th1 and Th2 cells are restricted to HLA-DQB1*0301. Even DQB1*0301 individuals without clinical evidence of BP have been found to have BP180-specific T cells, predominantly of the Th1 phenotype. Some studies have found that patients with BP have identical amino acid residues at positions 71–77 of their DQB1 gene.

**Nurture: Impact of Environmental Factors on Pemphigus and Pemphigoid**

As mentioned above, genetic predisposition alone is often not sufficient to promote development of pemphigus or pemphigoid. Environmental factors play a role in triggering autoimmunity in individuals with an underlying genetic predisposition. Medications, viral infections, allergens, radiation therapy, diet and emotional stress have all been reported to induce immune dysregulation, which may lead to a flare of pemphigus or pemphigoid in susceptible individuals.

With respect to medications, thiol-containing drugs such as penicillin, cephalosporins and captopril can bind to cysteine molecules in keratinocytes and interrupt cell–cell cohesion, causing a non-antibody-mediated pemphigus-like disease. These medications may also bind to desmogleins and other adhesion proteins causing them to adapt an altered conformation, which in turn precipitates the immune system to recognize them as “foreign,” eliciting production of DSG-specific antibodies. In drug-induced BP, thios may behave as haptens by binding to proteins within the basement membrane, stimulating production of anti-basement membrane antibodies. Foods high in thiols (garlic, leeks, onions) and polyphenols (black pepper, red chili pepper, cherry, red wine) are also thought to induce PV by a similar mechanism. BP, in comparison, has not been reported to have any dietary associations.
antigens. During the radiation-induced inflammatory event, leukocytes migrate to the lamina lucida, which may cause proteolytic cleavage and eventually, subepidermal bullae. Inhibition of Tregs may also contribute to the formation of an unregulated proinflammatory state and antibody production in both diseases.

Pesticide exposure has also been associated with PV onset. In an international survey of 126 pemphigus patients, 23.9% of them reported prior exposure to pesticides. The mechanism behind this association may be related to the activity of organophosphates on acetylcholinesterase. Organophosphate pesticides act by inhibiting the enzyme, acetylcholinesterase, which increases the concentration of acetylcholine. With prolonged exposure, the high concentration of the neurotransmitter will naturally induce a down-regulation of nicotinic and muscarinic receptors. As mentioned earlier, AChRs in the skin help regulate expression of desmogleins and thus a down-regulation of AChRs can lead to disruption of cell–cell adhesion. This mechanism also helps explain why cigarette smoking has been reported to have an inverse relationship with PV occurrence. Nicotine in tobacco activates nicotinic cholinergic receptors and thus may increase desmoglein expression.

Conclusions
A number of potentially causative factors, both genetic and environmental, have been proposed to influence the development of the autoimmune blistering diseases. The variety of inciting events and agents identified in the pathogenesis of these diseases is continually expanding. A detailed clinical history, especially with regard to medications, is important not only for identifying cases of drug-induced pemphigus but also for expanding our knowledge of environmental factors that may trigger the disease.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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How to cite this article: Patel F, Wilken R, Patel FB, Sultani H, Bustos I, Duong C, et al. Pathophysiology of autoimmune bullous diseases: Nature versus nurture. Indian J Dermatol 2017;62:262-7.
Received: November, 2014. Accepted: December, 2014.
Source of Support: Nil. Conflict of Interest: Nil.