CHRONIC BLISTERING DISEASES

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HISTORICAL PERSPECTIVE

Perhaps the oldest descriptions of what may have been a chronic blistering condition is in the Book of Job, Chapter 2, Verses 7 and 8: "... and he smote Job with running sores from head to foot, so that he took a piece of broken pot to scratch himself". Although the term "Job's syndrome" has been used in the modern medical literature for recurrent boils (furuncles) the presence of "running sores" and the suggestion of pruritus indicates that Job's disease was more likely a chronic blistering condition. Many other accounts of blistering diseases are well described by writers of the ancient world and middle ages. In most of these, the blisters were of brief duration and associated with fever, suggesting a diagnosis of herpes simplex, bullous impetigo or erythema multiforme.

The term pemphigus (Greek for bubble) was first used by Hippocrates (425 B.C.) in classifying a number of acute febrile blistering diseases. Until the 19th century both chronic and acute blistering diseases were classified under the single generic term Pemphigus (Figure 1). In 1791, Wichmann was the first to describe a patient with clinical features consistent with our current concept of pemphigus. The characteristic features of the case, as described by Wichmann in remarkable detail were:

> flaccid bullae in some instances and detachment of the epidermis without bullae formation in others resulting in large denuded areas of skin; severe involvement of the oral mucosa with extension to the vermilion border of the lips; and a fatal outcome.

Wichmann suggested that the word pemphigus be used for this case and other chronic bullous diseases and the term febris bullosa be used for blistering eruptions of short duration.

Pemphigus foliaceus was recognized as a distinct form of pemphigus by Cazenave in 1844 and by 1860, Hebra had separated the bullous form of erythema multiforme (erythema multiforme exudativum) from the pemphigus category. Erythema multiforme, an acute disorder, will be included in this discussion of chronic blistering diseases because it occasionally is mistaken for three of the chronic bullous diseases (i.e. dermatitis herpetiformis, bullous pemphigoid and herpes gestationis).

Duhring published the first of several papers describing dermatitis herpetiformis in 1884. He recognized this benign chronic blistering disease by the presence of symmetrical, intensely pruritic lesions that were urticarial, erythematous, vesicular, bullous, pustular or papular. From his description it is obvious that his group included not only what we now regard as dermatitis herpetiformis but also some forms of bullous pemphigoid. In addition, Duhring included herpes gestationis, previously recognized as a distinct entity by Milton in 1872, as part of dermatitis herpetiformis. Controversy over the distinction of dermatitis herpetiformis, pemphigoid, erythema multiforme, and herpes gestationis began with

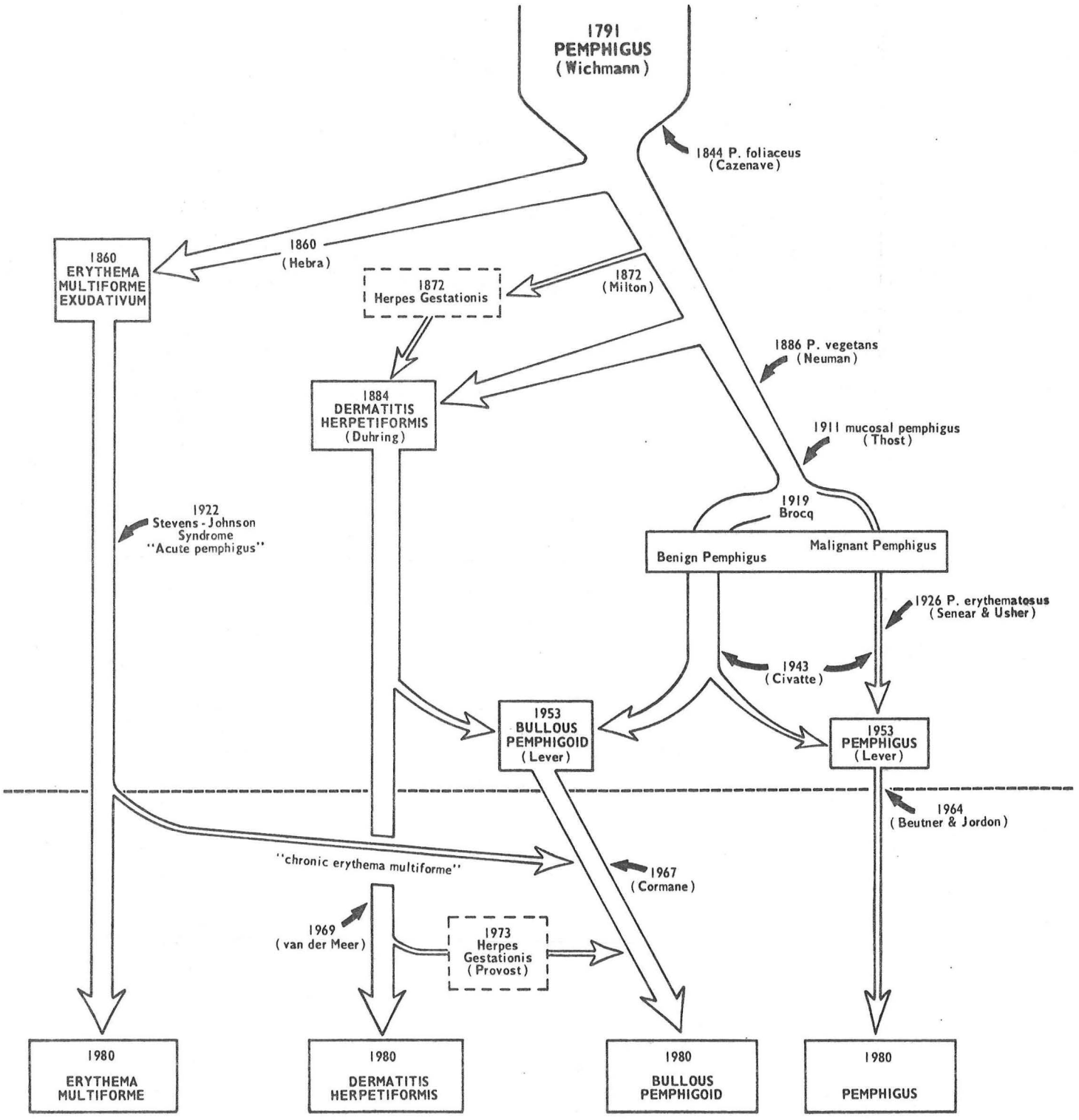

Figure 1, a schematic representation of the historical relationship between pemphigus and the other chronic blistering diseases. The conceptual change of pemphigus from a heterogenous group of ill-defined chronic blistering diseases in 1800 to a well characterized disease in 1980 is shown.

Duhring's description in 1884 and continued until the early 70's when the application of modern immunofluorescence and immunoelectron microscopic techniques led to a more precise definition of these conditions.

With the addition of pemphigus vegetans in 1886 by Neuman, pemphigus and its major variants were all well described and separated from erythema multiforme, dermatitis herpetiformis and herpes gestationis.

Brocq, in 1919, divided patients with pemphigus into two distinct categories, a chronic benign form and a malignant type. The important clinical differences between these two types were: 1) In the malignant form small flaccid bullae quickly ruptured to leave denuded areas which increased in size by detachment of the epithelium at the periphery, while in the chronic variety large tense blisters ruptured to leave erosions with no tendency toward peripheral extension. 2) Mucosal lesions were much more common and more severe in the malignant form than in pemphigus chronicus. 3) Mucosal lesions were often the first site of involvement in the malignant form but not in the chronic variety. 4) The mortality rate among patients with malignant pemphigus approached 100%. Chronic pemphigus was usually not fatal. Although several writers seemed to agree with Brocq's point of view, general acceptance of this division of pemphigus into two forms did not gain wide acceptance. It was not until 1943 when Civatte rediscovered and publicized the phenomenon of acantholysis, first described in 1881 by Auspitz, that pemphigus was further divided according to Brocq's suggestion.

The recognition that the bullae of the malignant form of pemphigus were formed by the loss of cellular adhesion producing a characteristic histologic change (acantholysis) permitted a clear distinction between the bullae of pemphigus and the other chronic blistering processes. Using this knowledge Lever examined the clinical and histopathologic features of 153 patients with pemphigus admitted to the Massachusetts General Hospital between 1937 and 1951. This led to the recognition of bullous pemphigoid, a chronic subepidermal blistering process with pemphigus-like features but with a more benign course. The findings of this study were published in an extensive paper filling the entire February 1953 issue of Medicine. The delineation of pemphigoid by Lever in clearly defined terms of clinical appearance, behavior, histology, response to treatment and prognosis convincingly demonstrated that it was an entity in its own right. Thus, by 1960, pemphigus, bullous pemphigoid, dermatitis herpetiformis (plus its presumed variant herpes gestationis) and erythema multiforme were generally recognized as distinct clinical entities.

In 1964, Beutner and Jordon discovered that the serum from most patients with pemphigus vulgaris contained antibodies to an antigen in the intercellular substance of stratified squamous epithelium. This finding opened a completely new era of immunologic investigation of skin diseases ultimately leading to the development of a new subdiscipline, immunodermatology.

In recent times both immunofluorescence and immunoelectron microscopic techniques have been used to identify several more subtle abnormalities which are regularly associated with these chronic blistering diseases. This has led to improved diagnostic methods and a better understanding of the pathogenesis of these disorders.

It is the purpose of this review to describe and compare the clinical, pathologic and immunopathologic features of these chronic bullous diseases which are historically linked to pemphigus. The following conditions will be discussed:

I. Erythema multiforme

II. Dermatitis herpetiformis

III. Pemphigoid

  A. Bullous pemphigoid

  B. Cicatricial pemphigoid

    1. Benign mucous membrane pemphigoid

    2. Chronic localized pemphigoid (Brunsting-Perry pemphigoid)

  C. Linear IgA subepidermal bullous dermatosis

  D. Herpes gestationis

IV. Pemphigus

  A. Pemphigus vulgaris and pemphigus vegetans

  B. Pemphigus foliaceus and pemphigus erythematosus

ERYTHEMA MULTIFORME

Erythema multiforme (EM) is an acute and frequently recurrent inflammatory syndrome with skin and mucous membrane lesions. In some severe cases constitutional symptoms and visceral lesions occur. The condition can be divided into two distinct clinical and histological varieties: (1) dermal EM with erythematous, macular and papular dermal inflammatory lesions, and (2) epidermal EM with erythematous macular and papulovesicular lesions showing prominent epidermal injury and/or necrosis. Bullous lesions in the first variety develop by excessive accumulation of edema fluid in the upper dermis resulting in a subepidermal blister lying beneath the epidermal basement membrane. In the second form, which is more often associated with bullous lesions, the blister develops above the epidermal basement membrane secondary to destruction of the epidermal basal layer. Epidermal EM is the variety which was described by Hebra as erythema multiforme exudativum (EME).

The etiology and pathogenesis of erythema multiforme is unknown. It appears to be a symptom complex secondary to many diseases and drugs which trigger a toxic or hypersensitivity reaction. The reported causes or associated diseases are listed below.

CAUSES OF ERYTHEMA MULTIFORME

1. Viral infections (Herpes Simplex)
2. Mycoplasma
3. Fungal infections (histoplasmosis, coccidiomycosis)
4. Bacterial infections (typhoid fever, BCG vaccination, leprosy, gonnococcemia, etc.)
5. Collagen diseases (lupus erythematosus, dermatomyositis)
6. Malignancy
7. Drugs

In children and young adults the eruption is most frequently associated with infections and in older persons with drugs or a malignancy. A more comprehensive list of causes of erythema multiforme has been compiled by Sontheimer, et al. (1978).

Clinical Manifestations

Two basic types of lesions are recognized. One is macular or urticarial and the other vesicular or bullous. The eruption appears suddenly and is symmetrical with a predilection for the backs of the hands, palms, soles, extensor surfaces of the limbs and mucous membranes. Involvement of the trunk follows the appearance of lesions on the extremities. The lesions tend to come in crops over a two to three week period. The most characteristic configuration is the so called "iris" or "target" lesion which is an erythematous or urticarial lesions with a dusky center (that may blister) surrounded by successive bright red rings.

The bullous lesions develop in the center of preexisting macules, papules or wheals and may involve the mucous membranes more than the skin. Oral lesions are present in 50% of patients and may be the only lesions in 25%. The conjunctiva are also affected. Conjunctival involvement is usually evident a few days after that of the skin and is always bilateral.

The Stevens-Johnson Syndrome is characterized by a sudden onset with severe mucous membrane as well as visceral involvement. There is usually a prodrome of 1-14 days consisting of fever, malaise, cough, sore throat, chest pain, vomiting, diarrhea, myalgias and arthralgias of variable severity. Mucous membranes of the mouth, tongue, lips, eyes, nasal mucosa, genitalia and rectum may be involved. The hemorrhagic crusting of the lips may be impressive. Rarely, hematuria, renal tubular necrosis and progressive renal failure may occur (Comaish and Kerr, 1961). This severe sometimes fatal multisystem form of the disease was first described in 1932 and is probably the same condition that was known as pemphigus acutus in the early 1900's.

Pathology

The microscopic picture of bullous EM is not diagnostic. A subepidermal bullous lesion with an upper dermal perivascular lymphocytic infiltrate is found. The degree of epidermal injury is prominent in the epidermal form and may show severe destruction of the basal layer with focal areas of epidermal necrosis. In the most severe forms of erythema multiforme the histologic picture may be identical to that seen in toxic epidermal necrolysis. Immunofluorescence studies have yielded variable results. Recent workers have published that vascular immunoglobulin deposits occur in some patients but the significance of this finding is unknown. Circulating antibodies to skin antigens are not found.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is a chronic, recurrent skin condition seen most often in young to middle-aged white men. It is characterized by marked pruritus and the symmetrical appearance of a polymorphic vesiculo-bullous eruption. Untreated the condition may last for years with remissions and exacerbations. Iodides may worsen the eruption. The general health is usually unaffected.

In 1966, Marks and coworkers, demonstrated an association of DH with partial or subtotal villous atrophy of the jejunal mucosa. The histologic features consisted of a flattened mucosa with inflammatory changes, essentially the same as seen in gluten sensitive enteropathy (GSE). In more recent studies a strong association between HLA-B8 and -DR3 has been found in patients with both GSE and DH (Katz SI, 1972). In view of the prevalent opinion that DH may be a cutaneous manifestation of gluten sensitivity several investigators have examined the effect of a gluten-free diet on the inflammatory skin condition. Beneficial effects have been reported from three studies (Harrington CI, 1977)(Heading RC, 1976)(Fry L, 1973).

Clinical Manifestations

The disease most frequently appears between the second and fifth decades. Men are affected twice as commonly as women. The disease is uncommon in blacks. DH has a sudden onset without prodromal constitutional symptoms. Pruritus and occasionally a burning sensation are usually the initial symptoms and may be intense. The early lesions are erythematous macules or papules that have superimposed vesicles. Bullae are rare and best appreciated in exacerbations that follow discontinuation of therapy. The lesions are remarkable in their symmetrical arrangement. Vesicles may be difficult to find because of their early excoriation. Occasionally lesions may assume an annular or gyrate pattern. The distribution of the lesions is over the extensor surfaces of the extremities, the elbows and knees, buttocks, sacral and scapular areas, and the scalp.

In 1940, Costello discovered that sulfapyridine dramatically suppresses DH. It was found to have no effect on pemphigus or erythema multiforme. The beneficial effect was so impressive that it became common practice to use sulfapyradine responsiveness as a test for the

diagnosis of DH. More recently di-amino-di-phenyl sulfone (DDS or dapsone), has proved to be at least as effective as sulfapyradine in treating this disease. A gluten-free diet may allow reduction or even discontinuance of dapsone therapy.

Few significant new observations have been made on the mechanism of action of sulfones. The early evidence from Millikan and Conway (1974) that dapsone may inhibit the alternative complement pathway could not be substantiated (Katz, S, 1977). Electron microscopic studies of clinically normal skin of patients under treatment with dapsone or a gluten-free diet revealed membrane bound vacuoles containing fibrillar material in the papillary dermis (Riches, et al., 1973). Early blisters developed in the papillary dermis with intact basement membrane above. In the patients under control on a gluten-free diet the papillary dermal vesicles were rarely seen, suggesting that dapsone suppresses the pathologic process to a "subclinical state", while the gluten-free diet actually returned the skin toward normal. These same authors in a follow-up study of patients after withdrawal of dapsone showed that the papillary dermal vacuoles seem to coalesce to form blisters suggesting that basement membrane changes, fibrin deposition and inflammatory cell participation are probably late events or secondary alterations (Riches DJ, et al., 1976).

The most recent study pertaining to the action of dapsone on the inflammatory response was published by Stendahl, et al. in 1978. These investigators found that dapsone blocked the myeloperoxidase-H_2O_2-halide system in normal polymorphonuclear leukocytes. They suggested that the beneficial effect of dapsone might result from the interruption of this PMN mediated cytotoxic mechanism which could be necessary for the expression of DH. This proposed mechanism, if substantiated, could tie together one of the major histologic features of DH (the presence of polys) and predictable clinical features (flares with ingestion of iodides and dapsone responsiveness).

Pathology and Immunopathology

The most characteristic finding is accumulation of polymorphonuclear leukocytes in the tips of dermal papillae leading to papillary necrosis and early epidermal separation or bullous formation. These papillary microabscesses are best seen in biopsies taken from an early erythematous lesion or at the margin of an early blister.

The first description of immunoglobulin deposits in the skin of patients with DH was by Cormane in 1967 (Cormane RH, 1967). He reported immunoglobulin in both involved and adjacent uninvolved skin although no mention of the immunoglobulin class was made. In 1969, van der Meer, reported IgA deposits and since then IgA has been consistently found in skin of essentially all patients with DH. Occasionally IgM and IgG may be seen as well. The immune deposits are generally in the papillary dermis and usually assume a granular pattern. Holubar and coworkers (1971) demonstrated the deposition of C3 in DH skin adjacent to lesions in the same pattern as IgA. More recent studies have shown that C1q and C4 are usually absent but factor B and properdin are frequently present suggesting complement activation by the alternative pathway (Provost TT, 1974).

Mowbray and coworkers (1973) first demonstrated circulating immune complexes in patients with DH. Serum complement levels are usually normal and other manifestations of immune complex mediated injury such as arthritis or glomerulitis have been rarely described (Combs RC, 1980). Two groups have recently shown that some dermatitis herpetiformis patients have circulating immune complexes containing IgA (Zone, et al., 1980) (Hall RP, et al., 1980) (see Figures 2 and 3). Zone and Provost (1980) have provided evidence that gliadin (an alcohol-soluble wheat protein) may be contained in the circulating immune complexes.

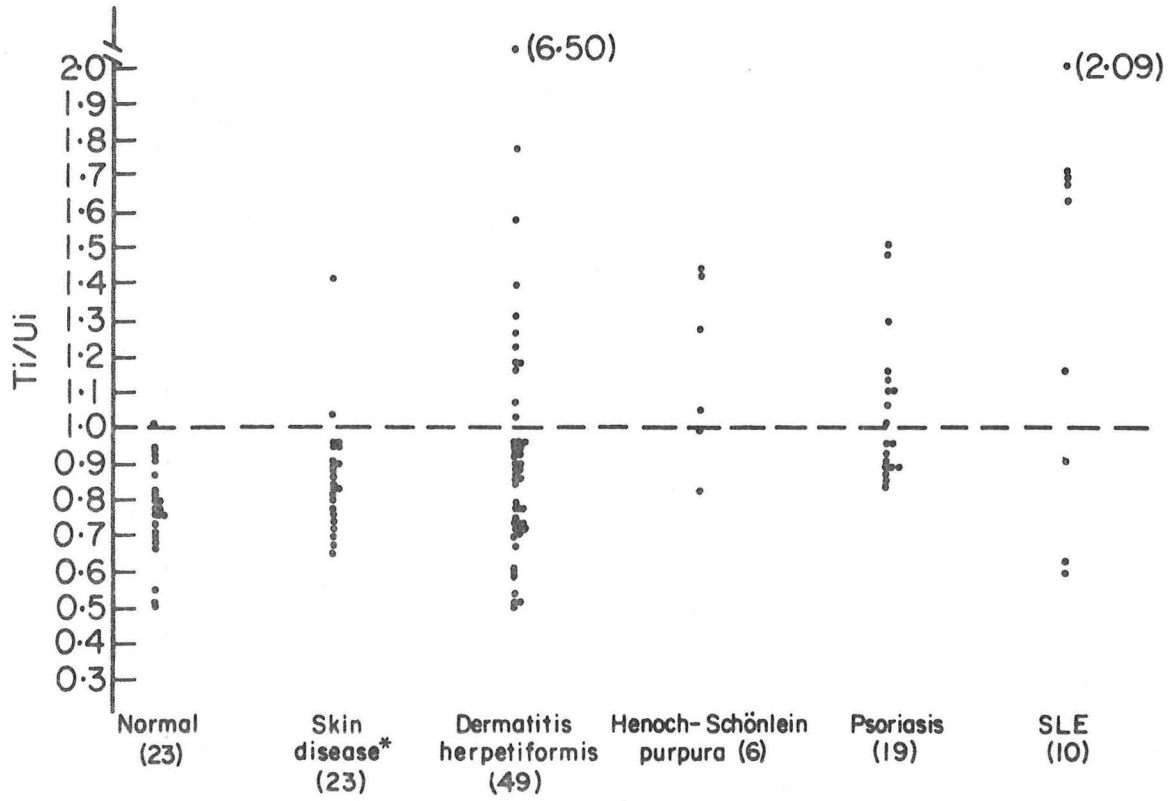

Figure 2. Levels of IgA immune complexes in patients with dermatitis herpetiformis (49 patients) IgA cic in 12/49 (24%) with DH.

$$\text{Ti/Ui} = \frac{\text{mean Raji cell-bound radioactivity after test serum}}{\text{mean Raji cell-bound radioactivity after norm. serum}}$$

(Hall RP, Lawley TJ, Heck JA and Katz SI: IgA-containing circulating immune complexes in dermatitis herpetiformis, Henoch-Schönlein purpura, systemic lupus erythematosus and other diseases. Clin Exp Immunol 40:431, 1980)

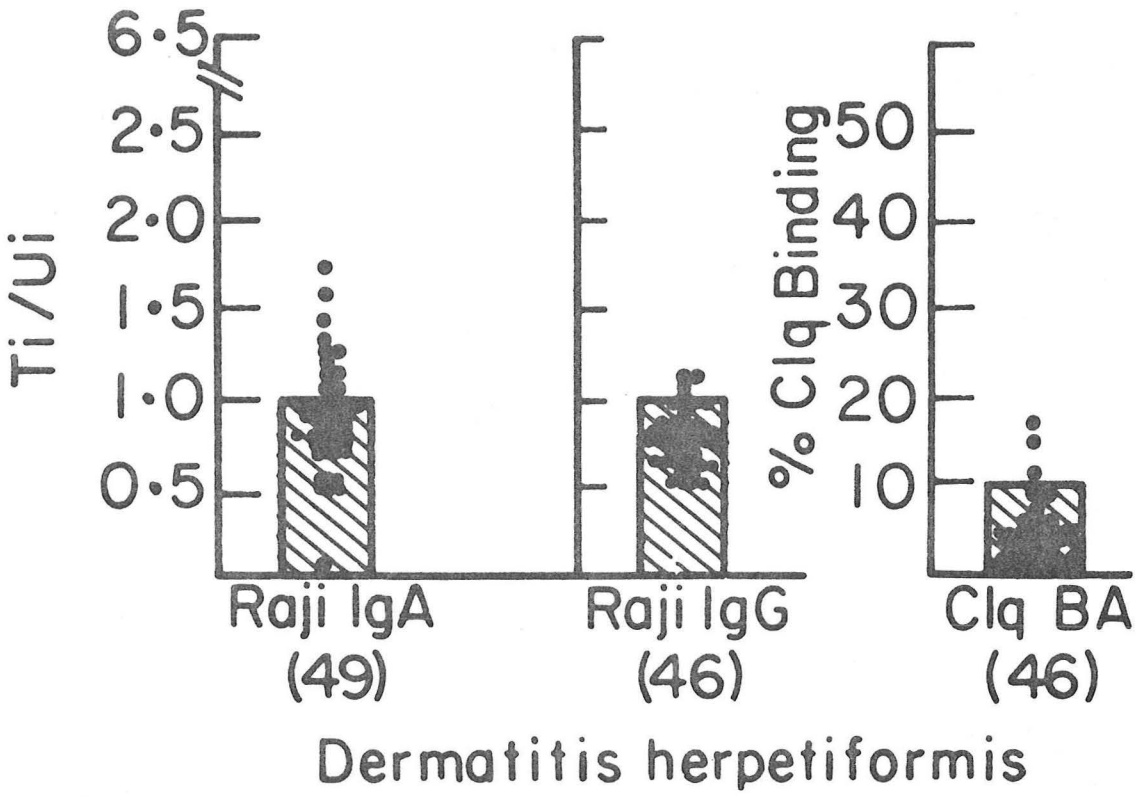

Figure 3. Comparisons of levels of immune complexes in patients with DH using the Raji IgA, the Raji IgG and the Clq binding radioassays. (Hall RP, Lawley TJ, Heck JA and Katz SI: IgA-containing circulating immune complexes in dermatitis herpetiformis, Henoch-Schonlein purpura, systemic lupus erythematosus and other diseases. Clin Exp Immunol 40:431, 1980)

Seah and coworkers (1972) have suggested that the immunoglobulin (IgA) deposits in the skin of patients with DH are bound to reticulin fibers. They have presented some evidence to suggest that antibodies to reticulin may cross-react with gluten and that serum from 17% of 29 patients with DH and 36% of 31 patients with celiac disease had reticulin antibodies (Seah PP, 1971). They have proposed that cross-reacting antibodies to small intestine reticulin initiate the pathologic events in celiac disease and that an analogous process occurs in the skin of patients with DH (Seah PP, et al., 1972).

Yaoita and Katz (1976) using immunoelectron microscopic techniques have demonstrated that IgA is deposited in clumps in the papillary dermis in DH. In those patients with linear deposits the antibodies are found either below the lamina densa (possibly on anchoring fibrils) or occasionally in the lamina lucida as seen in bullous pemphigoid (Figure 4a, 4b). Stingl and coworkers (1976) have suggested that papillary dermal IgA in DH appears to be bound to microfibrils or anchoring-fibrils always sparing the basal lamina (Figure 4c).

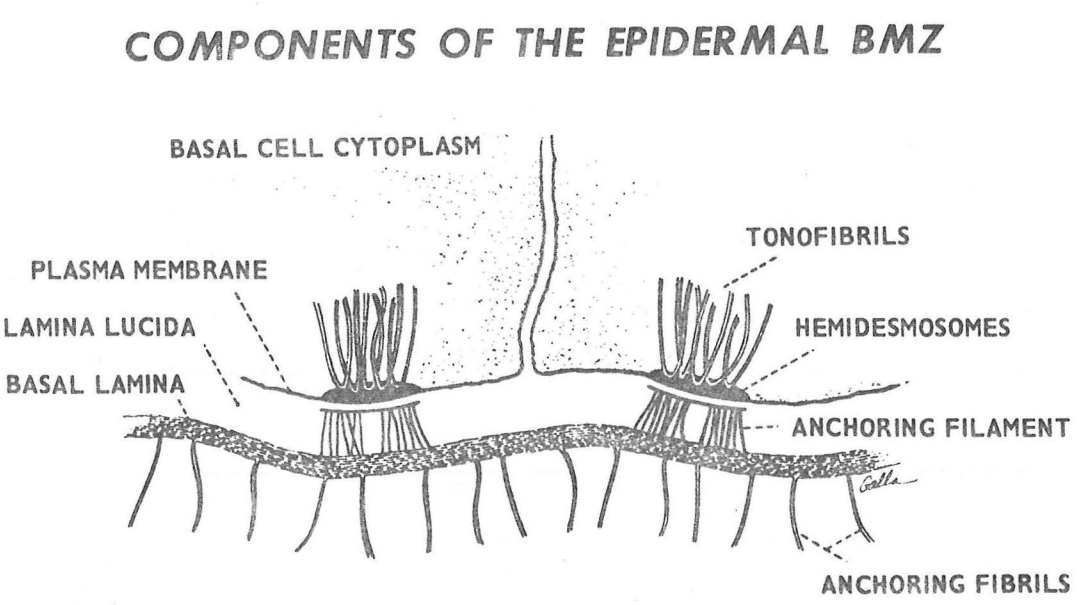

Figure 4a. Schematic representation of the dermal epidermal junction or epidermal basement membrane zone (BMZ). (Harrist TJ and Mihm MC: Cutaneous Immunopathology. Prog in Human Path 10:625, 1979)

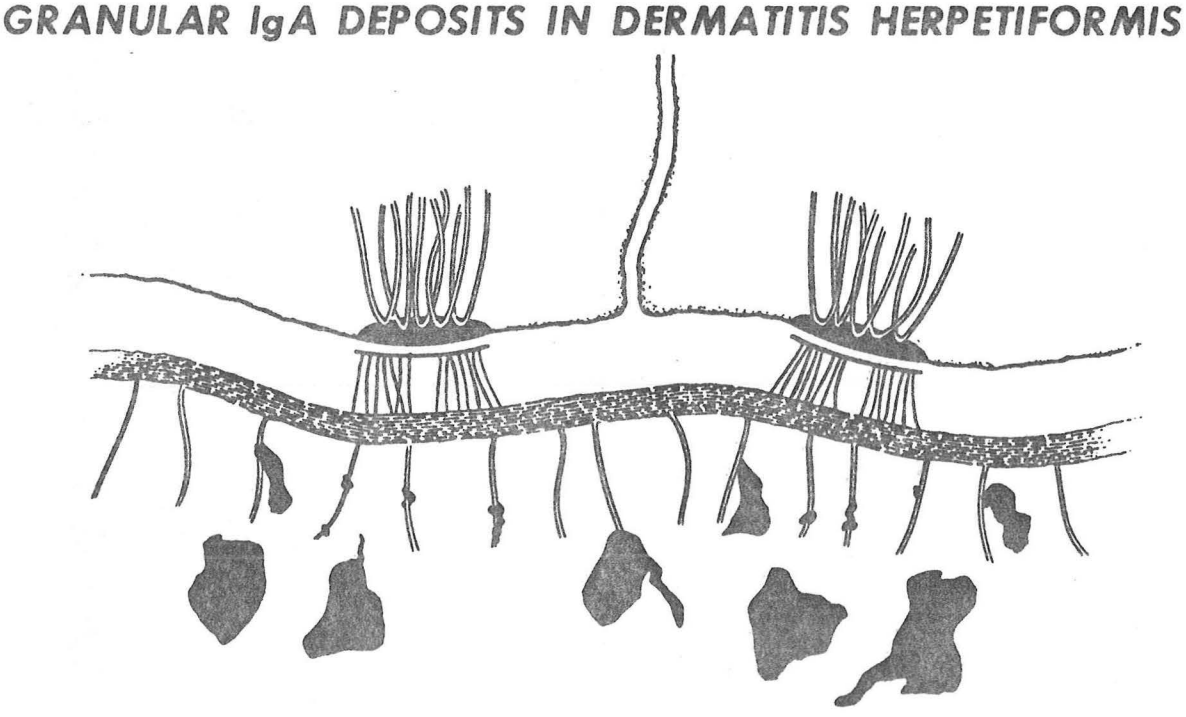

Figure 4b. Schematic representation of papillary IgA deposits (irregular clumps) in dermatitis herpetiformis. (Harrist TJ and Mihm MC: Cutaneous Immunopathology. Prog in Human Path 10:625, 1979)

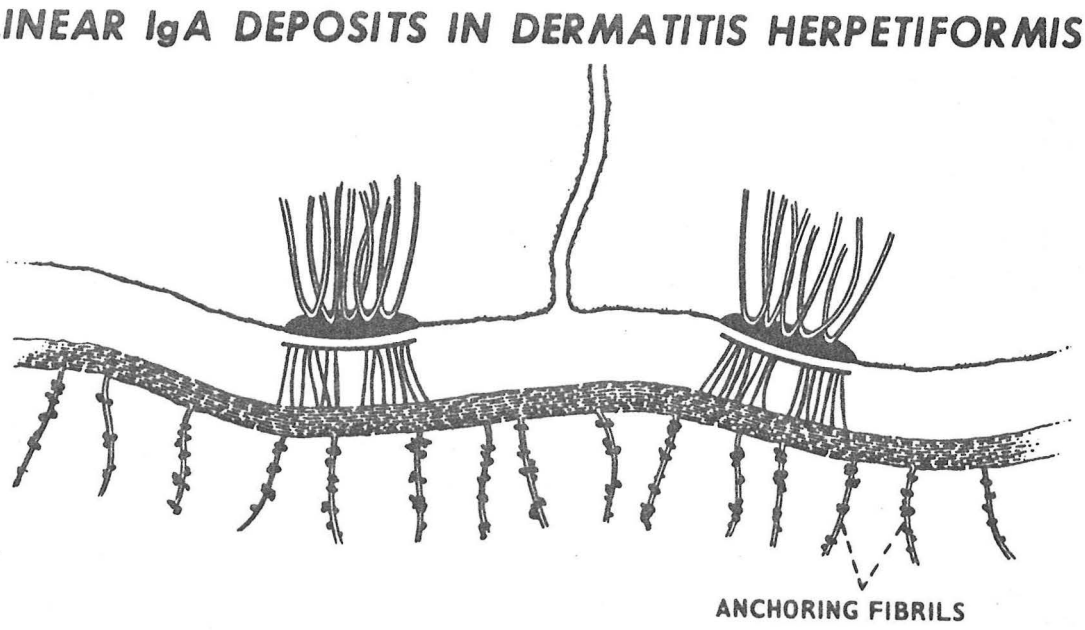

Figure 4c. Granular IgA deposits, associated with anchoring fibrils, as seen in dermatitis herpetiformis with linear pattern. (Harrist TJ and Mihm MC: Cutaneous Immunopathology. Prog in Human Path 10:625, 1979)

Proposed Pathogenesis of DH

A proposed scheme for the pathogenesis of DH is shown in Figure 5. Patients with a genetically predisposed hypersensitivity to gluten or some related wheat protein (gliadin) when exposed to dietary wheat

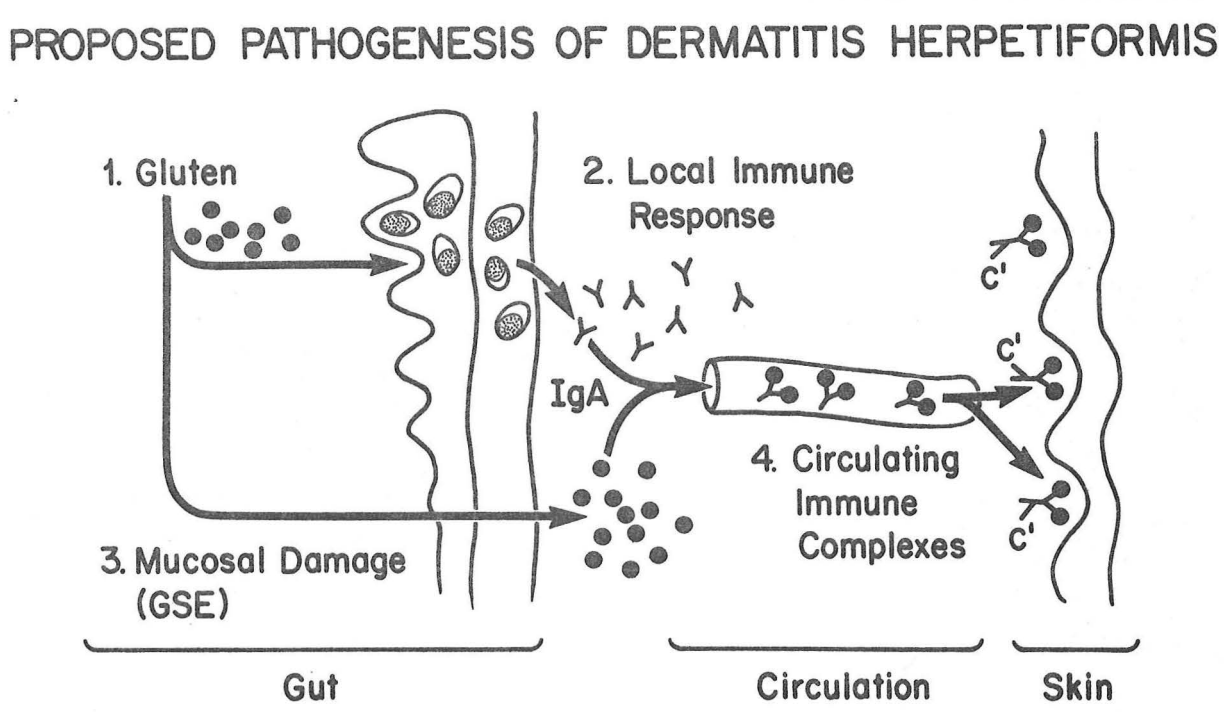

Figure 5.

develop an inflammatory lesion in the bowel wall with mononuclear cell infiltration and mucosal atrophy. This inflammatory reaction triggered by gluten is associated with an immune response to this inciting agent, leading to the local production of IgA anti-gluten antibodies. Immune complexes of IgA and gluten form in the gut, gain access to the circulation, go to the skin and bind in the papillary dermis. These IgA-antibody: antigen complexes then initiate an inflammatory response by activating the complement cascade via the alternative pathway thereby generating vasoactive and chemotactic factors. This inflammatory reaction is characterized by the accumulation of polymorphonuclear leukocytes in the area of immune complex deposition, the papillary dermis. An alternate hypothesis would be that the IgA anti-gluten antibody produced in the gut cross-reacts with collagen or reticulin fibers leading to binding of the IgA antibody to the connective tissue of the papillary dermis. The inability to demonstrate circulating antibody to a papillary dermal component in DH serum by indirect immunofluorescence is somewhat against this suggestion.

Dermatitis Herpetiformis -- Associated Diseases

Table I summarizes the evidence from the literature suggesting an association between DH and thyroid disease. The type of thyroid abnormality varies and includes idiopathic hypothyroidism, Graves disease, Hashimoto's thyroiditis and hyperthyroidism. This association may be due to a shared immunologic abnormality or possibly by common genetic factors in DH and thyroid disease related to the HLA-B8 and/or DR3 loci.

TABLE I

Thyroid disorders and dermatitis herpetiformis

Author	Age	Sex	Thyroid abnormalities	Thyroid antibodies	Relation to DH
1. Wise	34	M	Postthyroidectomy	ND	Rash followed thyroidectomy
2. Rattner et al	24	F	Thyrotoxicosis	?	Rash cleared with iodine
3. Smith	?	?	Thyrotoxicosis	ND	Rash cleared after thyroidectomy
4. Smith	?	?	Thyrotoxicosis	ND	Dapsone lowered after subtotal thyroidectomy
5. Smith	?	?	Thyrotoxicosis	ND	No change
6. Rostenberg et al	47	M	Idiopathic hypothyroidism	ND	Thyroid hormone aggravated DH
7. Goldin and Wilkinson	66	F	Post-^{131}I for Graves' disease	ND	No change with thyroid
8. Kumar	48	F	Thyrotoxicosis	+	No change with treatment
9. From and Thomsen	68	M	Idiopathic hypothyroidism on replacement	−	Iodine worsened rash
10. Douglas and Alexander	60	F	Post-^{131}I for thyrotoxicosis	ND	Thyroxine dose related to control of DH
11. Douglas and Alexander	70	M	Thyrotoxicosis	ND	Thyroxine dose related to control of DH
12. Douglas and Alexander	70	F	Post-^{131}I for thyrotoxicosis	ND	Thyroxine dose related to control of DH
13. Douglas and Alexander	36	F	Postthyroidectomy	ND	Thyroxine dose related to control of DH
14. Davies et al	51	F	Thyrotoxicosis (Graves')	+	Thyroid disorder preceded DH
15. Davies et al	44	M	Thyrotoxicosis (multinodular goiter)	−	Thyroid disorder preceded DH
16. Callen et al	18	M	Hyperthyroidism	+	Easier control of DH after thyroidectomy

ND: not done.

Table II lists examples of the coexistence of DH and abdominal lymphoma. All of these cases may be linked by the presence of gluten sensitive enteropathy since GSE has been previously allied with intestinal lymphoma. DH has also been associated (in sporatic case reports) with several other immunologic disorders. These include the following: lupus erythematosus (Vandersteen PR and Jordon RE, 1974)(Monacada B, 1974), rheumatoid arthritis (Kalimo K, 1978), ulcertive colitis (Davies, et al., 1978), Raynaud's phenomenon (Callen, et al., 1979), pernicious anemia (Tedesco, 1979)(Cream, 1970) and Sjogren's syndrome (Fraser, 1979). These findings lend some support to the theory that DH may represent a disease with altered immune reactivity.

TABLE II

Lymphoma and dermatitis herpetiformis

Report	Age	Sex	Type and site of lymphoma	Length of DH (yr)	GSE*
1. Gjone and Nodöy	44	M	Histiocytic—jejunum	17	+
2. Andersson et al	60	F	Histiocytic—mesenteric	40	+
3. Goodwin and Fry	57	M	Histiocytic—jejunum	25	+
4. Fowler and Thomas	59	M	Lymphocytic—skin	7	+
5. Gould and Howell	60	M	Histiocytic—jejunum	19	+
6. Silk et al	51	M	Histiocytic—jejunum	14	+
7. Freeman et al	60	M	Histiocytic—stomach	20	+
8. Freeman et al	42	M	Histiocytic—jejunum	½	+
9. Freeman et al	62	M	Undifferentiated—multiple sites throughout small intestine	5	+

*Clinical or histologic evidence of GSE.

(Gjone E, Nordoy A: Brit Med J 1:610, 1970; Andersson H, Dotevall G, Mobacken H: Scand J Gastroenterol 6:397, 1971; Goodwin P, Fry L: Proc R Soc Med 66:625, 1973; Fowler JM, Thomas DJB: Brit Med J 2:757, 1976; Gould DJ, Howell R: Brit J Dermatol 96:561, 1977; Silk DA, Mowat NAG, Riddel RH, et al.: Brit J Dermatol 96:555, 1977; Freeman HJ, Weinstein WM, Shnitka TK, et al.: Am J Med 63:585, 1977)

PEMPHIGOID GROUP

Bullous Pemphigoid (BP) is a chronic subepidermal blistering disease without acantholysis. Pemphigoid commonly occurs in the elderly (Figure 6). More than 80% of the patients are over 60 years of age when the disease develops. It is now well known that patients with active bullous pemphigoid usually possess a serum antibody (almost always IgG) specific for the basement membrane zone (BMZ) of stratified squamous epithelium (Beutner EH, et al., 1968B). Approximately 70% of patients with pemphigoid have serum anti-BMZ antibodies and a higher percentage have immunoglobulin (IgG) fixed in vivo. Complement is also bound to the epidermal basement membrane and it seems likely that this plays an important role in initiating and focusing the inflammatory response at the dermal epidermal junction. Unlike pemphigus there is no relation between the extent of the disease in the skin and the titer of antibodies in the serum.

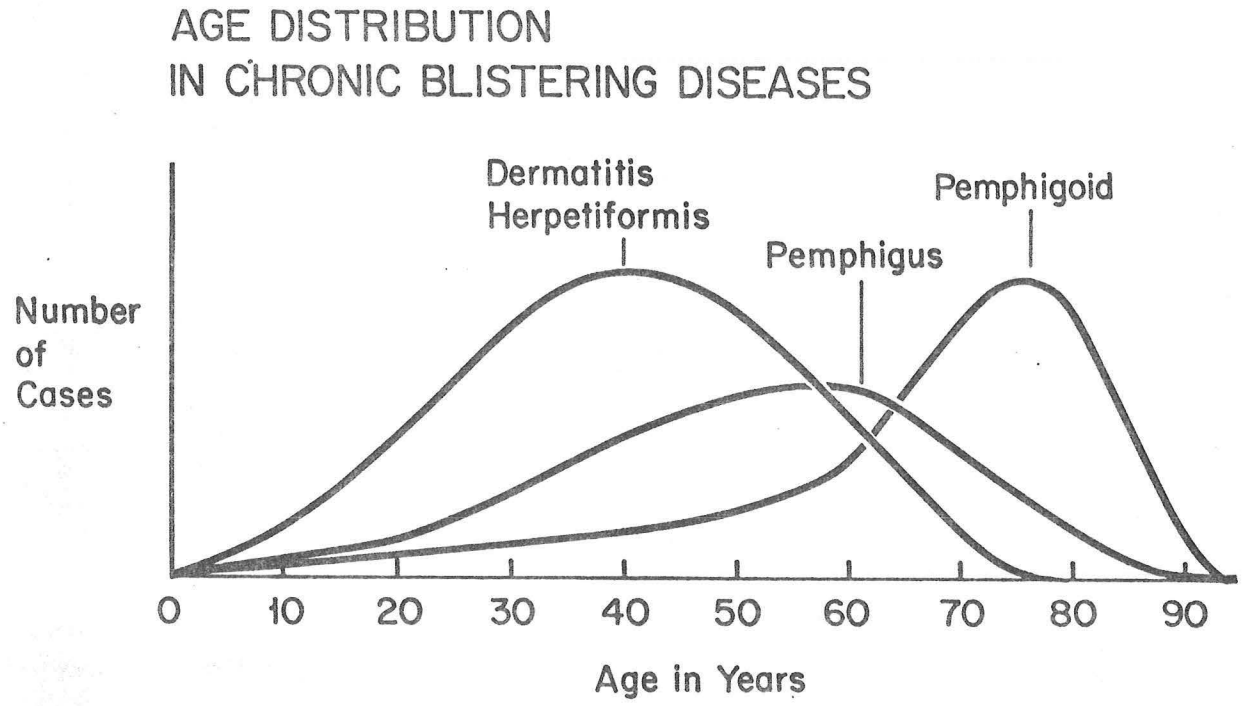

Figure 6.

Clinical Features

Bullous pemphigoid often starts as a rather nonspecific urticarial or eczematous eruption on the extremities. The erythematous or urticarial stage may last one to three weeks before blisters develop. When the lesions begin as an eczematous eruption blisters may not form for several months. Localized lesions often occur at a site of some preexisting skin disease such as stasis dermatitis or a burn scar. The periumbilical area is another common site of early involvement. Such localized lesions may remain confined to one area of the skin for as long as two years. Other commonly involved sites are the flexor forearms, the wrist, the anterior or medial aspect of the thighs, the groin and the pubic area. Approximately 75% of patients will complain of pronounced itching or a burning sensation. A diagnosis of erythema multiforme may be entertained when the initial lesions are nonbullous and consist of erythematous macules or papules, wheals or plaques. Occasionally these lesions assume an annular or even a target-like appearance. The bullous lesions of pemphigoid are usually large (two to three centimeters across), tense and do not rupture easily. They vary not only in size but also in shape and in this respect may resemble the smaller vesicular lesions of dermatitis herpetiformis which are often irregular in outline.

The frequency of mucosal involvement is variable. One-third of Lever's patients had mild oral lesions. In contrast to pemphigus, oral mucosal lesions rarely preceed the skin lesions in pemphigoid (Lever WF, 1953).

Pathology and Immunopathology

According to van der Meer (1972) most authors now recognize two histological types of pemphigoid called by some "infiltrate poor" and "infiltrate rich" forms. These have also been referred to as monomorphic and polymorphic as a reminder that the former picture is associated with a purely blistering skin disease whereas the latter also shows erythematous, papular, circinate and polycyclic lesions. The monomorphic type shows edema in the dermal papillary layer early followed by a small narrow fissure at the dermal-epidermal interface which enlarges under the influence of increased fluid pressure to produce a bullous lesion. There is little inflammatory reaction and the blister will have only a scanty cellular content. The superficial blood vessels have a cuff of lymphocytes and a few eosinophils. The peribullous skin of untreated patients often shows a single row of eosinophils lying close to the epidermal basement membrane. These cells are closely applied to the undersurface of the epidermis, the site of blister formation. There are no microabscesses in the papillae and in contrast to DH eosinophils are the predominant cell type. The PAS positive basement membrane (i.e. the lamina densa-anchoring fibril complex plus immature superficial dermal collagen) always lies on the floor of the bullous lesions. The floor of the bullae retains its convoluted (papillary) outline.

The polymorphic type has a different histologic picture. There is a dense cellular infiltrate in the papillary layer of the dermis composed primarily of eosinophils, lymphocytes and histiocytes. Some neutrophils are also present, but the cells immediately adjacent to the basal layer

of the epidermis are always eosinophils. The fully established blister quickly becomes populated with numerous eosinophils, lymphocytes and histiocytes. Papillary microabscesses may form at the margin at the bullous lesion making the distinction between BP and DH herpetiformis difficult, but the absence of papillary necrosis and the predominance of eosinophils suggest BP.

Table III summarizes the immunopathologic findings in the pemphigoid group. Over 70% of patients with active BP will have circulating antibodies that bind to the basement membrane of a variety of stratified epithelial substrates. The antibody is usually IgG, however, IgA, IgM, IgD and IgE have also been identified in a few cases. Both immunoglobulin and

TABLE III

IMMUNOFLUORESCENCE FINDINGS IN THE PEMPHIGOID GROUP

Disorder	% pos. DIF*	Binding site	Principle Immunoreactants	% pos. IIF**
Bullous Pemphigoid	∿100%	BMZ (lamina lucida)	IgG & C3	70%
Cicatricial Pemphigoid	65-85%	BMZ (lamina lucida)	IgG & C3	uncommon
Herpes Gestationis	∿100%	BMZ (lamina lucida; BC*** plasma membrane)	C3 (rarely IgG)	rare
Linear IgA Bullous Dermatosis	unknown	BMZ	IgA	rare

* DIF - direct immunofluorescence

** IIF - indirect immunofluorescence

*** BC - basal cell

complement (C3) can be identified along the basement membrane from lesional biopsies in almost all patients. Occasionally complement will be found in lesions without detectable immunoglobulin, as is usually seen in herpes gestationis. Immunoelectron-microscopic studies have localized the immune deposits in BP to the lamina lucida area (Figure 7).

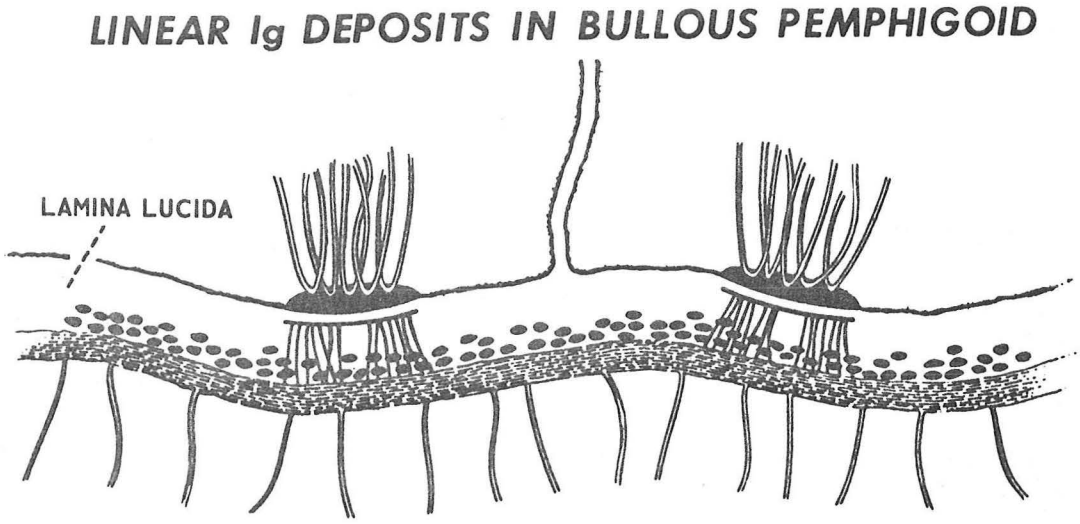

Figure 7. Schematic diagram of the deposition of immunoglobulin and complement in bullous pemphigoid. (Harrist TJ and Mihm MC: Cutaneous Immunopathology Prog in Human Path 10:625, 1979)

Bullous Pemphigoid -- Associated Diseases

In spite of the numerous case reports that have suggested an association between BP and internal malignancy, two studies from the Mayo Clinic have failed to substantiate this association (Stone, et al., 1975)(Person and Rogers, 1977).

Bullous pemphigoid has also been associated with a number of autoimmune diseases. This and the presence of anti-BMZ antibodies has been used as evidence to support the theory that BP should be considered to be an autoimmune disease. Rheumatoid arthritis has been the most commonly associated condition, as summarized in Table IV. In a report of 94 cases of bullous pemphigoid, Savin (1979) found eleven with rheumatoid arthritis. Such findings have suggested that this relationship is more than coincidental and that both exist because of a similar or related underlying abnormality.

TABLE IV

Pemphigoid and rheumatoid arthritis (RA)

Author	Age	Sex	Type of pemphigoid	Criteria used for diagnosis of RA	Duration of RA (yr)	Rheumatoid factor	Other disorders
1. Lillicrap	56	M	BP	Yes	12	Positive	No
2. Salo and Rasanen	68	F	BP	?	?	1:1,000	?
3. Salo and Rasanen	76	F	BP	?	?	1:32	?
4. Salo and Rasanen	69	F	BP	?	?	ND	?
5. Salo and Rasanen	53	F	BP	?	25	?	?
6. Salo and Rasanen	?	?	BP	?	?	1:32	?
7. Person and Rogers	?	?	BP	?	?	?	?
8. Person and Rogers	?	?	CP	?	?	?	?
9. Callen et al	70	F	BP	Yes—definite	43	1:2,560	PA
10. Spigel and Winkelmann	56	F	CP	Yes—definite	30	ND	No
11. Spigel and Winkelmann	67	M	CP	Yes—definite	4	1:2,560	No
12. Spigel and Winkelmann	80	M	CP	Yes—definite	2	Negative	No
13. Spigel and Winkelmann	78	M	CP	Yes—definite	50	1:2,80	No
14. Giannini et al	68	M	BP	Yes—definite	35+	1:1,000	No
15. Goodnough and Muir	81	F	BP	Yes	30	Negative	CLL

ND: not done.

(Lillicrap DA: Proc R Soc Med 56:921, 1963; Salo OP, Rasanen JA: Ann Clin Res 4:173, 1972; Person JR, Rogers RS: Mayo Clin Proc 52:54, 1977; Callen JP, Anderson TF, Chanda JJ, Taylor WB: Arch Dermatol 114:245, 1978; Spigel GT, Winkelmann RK: Arch Dermatol 114:415, 1978; Giannini JM, Callen JP, Gruber GG: submitted for publication, 1980; Goodnough LT, Muir A: submitted for publication, 1980)

Bullous pemphigoid has also been reported in patients with lupus erythematosus (Jordon, et al., 1969A)(Miller, et al., 1968)(Hermann, et al., 1978), pernicious anemia, thyroiditis (Callen, 1978), primary biliary cirrhosis (Hamilton and MacKenzie, 1978) and polymyositis (Peck and Lefkovits, 1966). Case IV (see Appendix) describes a patient that we have recently seen with both SLE and bullous pemphigoid.

PEMPHIGOID VARIANTS

The pemphigoid group can be divided into several subtypes as shown in Figure 8 and Table IV. These include localized chronic pemphigoid, desquamative gingivitis, cicatricial pemphigoid (benign mucosal pemphigoid and localized chronic or Brunsting-Perry pemphigoid), vesicular pemphigoid, linear IgA subepidermal bullous dermatosis and herpes gestationis. Of these pemphigoid variants the ones that deserve special consideration are cicatricial pemphigoid, linear IgA bullous dermatosis and herpes gestationis.

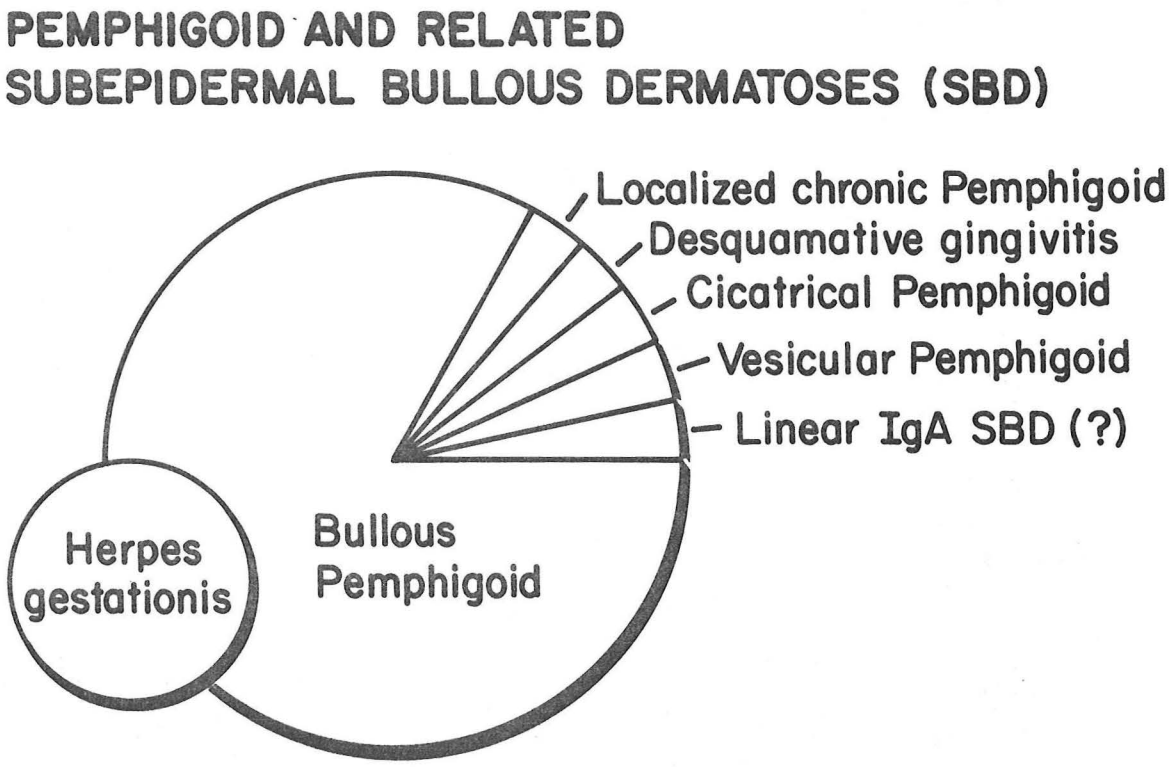

Figure 8.

TABLE V

PEMPHIGOID VARIANTS

I. Localized chronic pemphigoid (Brunsting-Perry pemphigoid)
A chronic localized subepidermal bullous process usually occurring on the head or neck region. Follows a chronic recurrent course. Usually spares the mucous membranes. Direct immunofluorescence (DIF) is positive for IgG and/or C3 at the BMZ. Circulating anti-BMZ antibodies rarely found. (Brunsting LA and Perry HO, 1957)

II. Desquamative gingivitis
DG produces chronic inflammation, edema, erythema and vesciulo-bullous lesions followed by gingival erosions. Light microscopy reveals subepithelial blister formation and DIF shows IgG or C3 at the BMZ. (Sparrow GP and Moynahan EJ, 1976)

III. Cicatricial pemphigoid (benign mucosal pemphigoid)
CP is a chronic subepidermal bullous eruption of the mucous membranes. IgG and C3 are found at the BMZ but circulating anti-BMZ antibodies are rarely present.

IV. Vesicular Pemphigoid
A dermatitis herpetiformis-like variant of bullous pemphigoid. Direct and indirect immunofluorescence typical of bullous pemphigoid. (Bean SF, et al., 1976)

V. Linear IgA subepidermal bullous dermatoses (IgA bullous pemphigoid) (Jones RR and Goolamali SK, 1980)
A subepidermal bullous disease with mixed clinical features of DH and BP. No evidence of GSE and not associated with HLA-B8 and/or DR3. Responds to combined prednisone and sulfone treatment. DIF shows linear IgA along the BMZ. Childhood (Chronic Bullous Dermatosis of Childhood) and adult forms have been described. (Polymorphic pemphigoid) (Honeyman JF, et al., 1979)(Chronic Bullous Dermatosis of Childhood)(Prystowsky SD and Gilliam JN, 1976)

VI. Herpes gestationis (HG)
Subepidermal blistering disease of pregnancy. Immunopathologic studies show C3 (occasionally IgG) at the BMZ. Appears to be hormone dependent. Injury may be eosinophil mediated.

These bullous pemphigoid variants (see Table V) have been so considered because of similarities in pathology and immunopathology. Whether they all represent different forms of BP remains controversial and many regard them as distinct entities with pathogenic mechanisms that happen to involve the same or a closely related anatomical site (i.e., the dermal-epidermal junction). For the purposes of this discussion they will be considered as part of the pemphigoid group as illustrated in Figure 9.

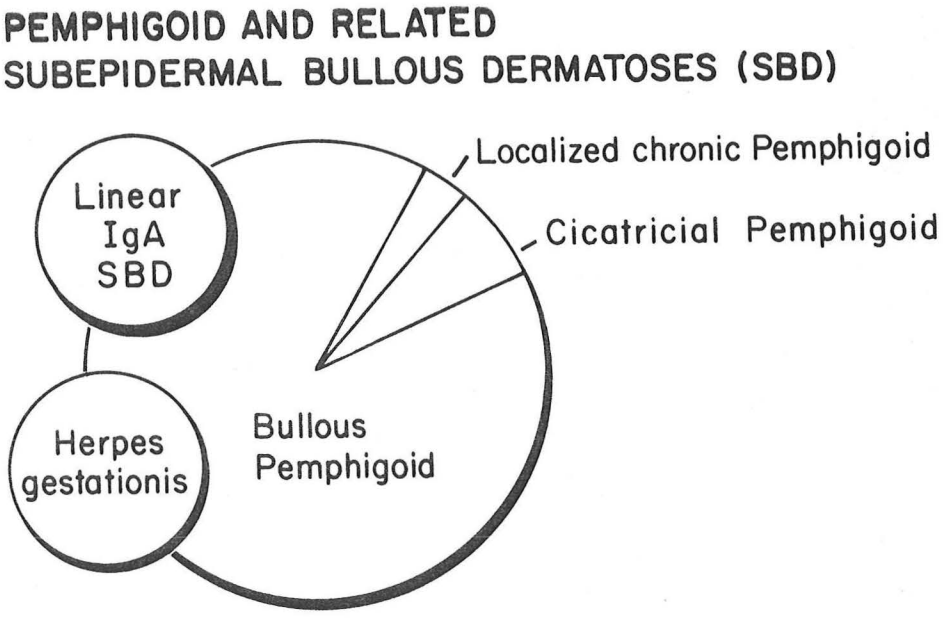

Figure 9.

Localized Chronic Pemphigoid

In 1957 Brunsting and Perry reported seven patients with an unusual recurrent, pruritic vesiculobullous eruption of the head and neck area which generally remained localized and eventually resulted in atrophic scars. A relation to benign mucosal pemphigoid or cicatricial pemphigoid was suggested even though mucous membrane involvement in these cases was absent or minimal. The name benign pemphigoid or Brunsting-Perry Pemphigoid has been used by most people to identify this unusual form of localized chronic pemphigoid.

Cicatricial Pemphigoid (Benign Mucosal Pemphigoid)

Cicatricial pemphigoid (formerly known as benign mucosal pemphigoid or ocular pemphigus) is a chronic recurrent blistering disease of the mucosa and skin which results in permanent scarring. The conjunctival involvement frequently leads to blindness. As in BP, cicatricial pemphigoid is a disease primarily of the aged, the average age of onset being over 60 years.

The onset of cicatricial pemphigoid is gradual and insidious. The initial lesions occur most commonly on mucosal surfaces, however, the skin is sometimes the initial site of involvement. Rarely the disorder begins simultaneously on skin and mucosa. Two types of cutaneous lesions may be seen. The most common is a generalized bullous eruption similar to that seen in BP but of short duration. The second is more localized and persistent. The oral mucosa, conjunctiva, mucous membranes of the larynx, esophagus, nose, penis, vulva, and anus may be involved.

The oral mucosa is involved in most cases and, as in pemphigus, may be the only area affected at the onset of the disease. Large denuded areas in the mouth differ from those seen in pemphigus vulgaris in that they usually do not show shreds of epithelium at the border and therefore appear cleaner. Unlike pemphigus they do not tend to bleed easily and they are less painful so that they do not interfere with eating. The vermilion border of the lip, which is a common site for lesions of pemphigus vulgaris, is only rarely involved in cicatricial pemphigoid. However, it is only by careful clinical, histologic and immunopathologic examination that cicatricial pemphigoid can be reliably differentiated from pemphigus. Table VI lists other causes of oral mucosal erosions that may cause some confusion in diagnosis.

In rare instances esophageal strictures will cause dysphasia. X-ray examination of the esophagus after barium swallow reveals one or several areas of constant narrowing at the site of stricture. The early adhesions may be dislodged and severe stenosis prevented if recognized. Thus, any patients with cicatricial pemphigoid complaining of dysphasia should have a barium swallow to assess the possibility of early esophageal involvement.

An extensive clinical and pathologic review of 81 patients with benign mucous membrane pemphigoid or cicatricial pemphigoid was published in 1971 by Hardy and coworkers. The following conclusions were derived from that study: 1) Mucosal involvement usually predominates over skin involvement. 2) disability generally develops from scarring. Laryngeal scarring causing a life threatening situation occurred in only two of 81 patients. 3) Although inflammatory lesions are annoying they seldom cause disabling disease. 4) There were no spontaneous remissions in this group followed for an average of six years. 5) Oral mucosa and conjunctivae were eventually involved in 75% of the cases. 6) Of the 81 patients 21 became blind, 17 in both eyes. 7) Systemic administration of cortico-steroids at a dose greater than 40 mg of Prednisone a day was the only treatment that seemed beneficial. 8) There were no deaths attributable to cicatricial pemphigoid but one patient died from the side-effects of corticosteroid therapy.

The relationship between cicatricial pemphigoid and BP continues to be poorly understood. Both show subepidermal blisters and in vivo binding of IgG and C3 to the epidermal basement membrane zone. The local persistence of lesions and the tendency to scar are unique to cicatricial pemphigoid. The scarring suggests a deeper dermal destructive inflammatory process that is not apparent in the typical case of bullous

TABLE VI

INVOLVEMENT IN EROSIVE MUCOSAL DISEASES

Disease	Usual age of onset, years	Sites of mucosal involvement†	Course		Histopathology	DIF Immunopathology	IIF
			Onset	Duration			
Pemphigus vulgaris	40-60	Buccal mucosa Pharynx Tongue Larynx Gingivae	Gradual	Years	Intraepidermal bulla Suprabasal cleft Acantholysis	ICS antibody specific or diagnostic findings	Pos. ICS-ab
Primary herpetic gingivostomatitis	1-25	Lips (buccal sulcus) Buccal mucosa Gingivae Tongue	Acute	10-14 days	Intraepidermal vesiculation Ballooning degeneration epidermal cells Epidermal multinucleated giant cells	Non-specific	Neg.
Recurrent aphthous stomatitis	10-30	Buccal mucosa Lips (buccal sulcus) Pharynx Genitalia Sclerae	Recurrent episodes	Years	Epidermal necrosis Lymphocytic and polymorphonuclear dermal infiltrate	Non-specific	Neg.
Cicatricial (mucosal) pemphigoid	More than 60	Conjunctivae Gingivae Buccal mucosa	Gradual	Years	Epidermis intact Subepidermal bulla	BMZ antibody diagnostic	BMZ-Ab rarely
Erythema multiforme	5-20	Lips Buccal mucosa Tongue Conjunctivae Urethral meatus and/or vagina Anus	Acute	2-3 weeks	Epidermal degeneration Intraepidermal vesiculation Subepidermal bulla Perivascular lymphocytic infiltrate	Non-specific	Neg.
Lichen planus	40-60	Buccal mucosa Tongue Gingivae	Insidious	Years	Basal cell hydropic degeneration Subepidermal bulla Dense papillary dermal lymphocytic infiltrate	Non-specific	Neg.

† Mucosal surfaces are listed in the usual frequency of involvement.

pemphigoid. Whether this stems from a different etiopathogenesis or is due to some undefined host related factor is unknown. Mondino and coworkers (1978) have recently found an increased frequency of HLA-B12 in patients with cicatricial pemphigoid (45%) which is statistically significant when compared to a frequency of 19.6% in the general population ($P < 0.02$). A weaker association was found between HLA-A3 and cicatricial pemphigoid. These findings suggest that HLA-B12 and possibly HLA-A3 are genetic markers for ocular cicatricial pemphigoid. In contrast, Ahmed and coworkers (1980) were unable to find a significant increase in a specific HLA type among nineteen white patients with BP. However, the frequent presence of linear basement membrane zone staining in cicatricial pemphigoid and the occasional presence of circulating anti-BMZ antibodies suggests that cicatricial pemphigoid and BP are variants of the same disease (Rogers RS, et al., 1977)(Bean SF, 1974).

Linear IgA Bullous Dermatosis

Patients with linear IgA deposits at the dermal epidermal junction have been considered by some to have a condition related to DH and by others to have a disease more like BP. Electron microscopic studies have shown that the antibody is usually localized to the lamina lucida area of the basement membrane zone (see Figure 4a). This is analogous to the site of IgG localization in patients with BP suggesting that the antibody is directed to a similar or perhaps identical BMZ component. Lawley and Katz (1980) have found that patients with this immunopathologic finding are unlike patients with DH in that they do not have an increase in HLA-B8 or -DR3 and they have no evidence of gluten sensitive enteropathy. These findings lend further support to the concept that linear IgA deposits in the lamina lucida are found in a disease process distinct from DH. Chronic blistering diseases with linear IgA deposits at the dermal-epidermal junction of lesional skin biopsies may occur in both children and adults.

Linear IgA Bullous Dermatosis of Adults

Adults with chronic blistering diseases and linear IgA deposits frequently show a mixed clinical picture. Often such patients not only have small papules and vesicles in a typical DH-like, herpetiform arrangement, but they also have large blisters of the type usually seen in BP. The response to sulfapyradine or sulfones is often dramatic during the initial phases of the disease but soon the process become progressively more unresponsive. Some authors have suggested that these patients have atypical forms of either DH or BP, however, in reviewing cases in the literature it appears that they consitutue a clinically distinct group. Honeyman and coworkers (1972)(1979) have described the clinical features and course of patients with linear IgA bullous dermatosis. They concluded from their observations that such patients more closely resemble BP than DH. herpetiformis. The following table shows the comparison of clinical and laboratory features between typical DH and linear IgA subepidermal bullous dermatosis (see Table VII).

TABLE VII

COMPARISONS OF TYPICAL DH AND LINEAR IgA BULLOUS DERMATOSIS

	Typical DH	Linear IgA Bullous Dermatosis
Characteristics of lesions	Papules and vesicles, grouped in typical distribution	Vesicular and bullous eruptions with grouping but usually not with typical distribution
Histology	Microabscesses in dermal papillae	Microabscesses in some but not all lesions
Jejunal changes	Usually present	Not found
Gluten free diet	May be effective	Not effective
Responses to sulfones and sulfapyridine	Dramatic responses usually throughout the course of the disease	Usually dramatic responses at the beginning but later in the course of the disease, steroids need to be added for control.
Immunofluorescence of biopsies of normal or erythematous skin	Granular or fibrillar deposits predominantely of IgA in dermal papillae	Linear deposits at the BMZ predominantely of IgA
Serum finding	No circulating BMZ antibodies	IgA class BMZ antibodies in some cases
Immunoelectronmicroscopy	IgA deposits in dermal papillae below BMZ	IgA deposits in the BMZ (lamina lucida)
HLA types	HLA-B8 pos. > 85%	HLA-B8 not increased

Linear IgA Bullous Dermatosis of Childhood

The chronic nonhereditary blistering diseases of childhood have posed special problems in diagnosis because they are rare and often confused with the more common acute blistering diseases. In recent years the histologic and immunopathologic features of these disorders have led to frequent changes in classification. Pemphigus, bullous pemphigoid and dermatitis herpetiformis are identical to the adult form of the disease and a number of cases of these disorders in children have been reported and reviewed (see Table VII)(Jordon, et al., 1973).

TABLE VIII

DIFFERENTIAL DIAGNOSIS OF NON-FAMILIAL CHRONIC BULLOUS DERMATOSES OF CHILDHOOD

Disease	Clinical Findings	Course and Treatment	Serology (IIF)	Immunopathology (DIF)
Benign chronic bullous dermatosis (linear IgA)	Large tense bullae on Lower trunk, extremities, genitalia; Rosettes often seen	Self limited, Relapsing; May respond to sulfones	Anti-skin BMZ abs. rarely present	Linear IgA along BMZ
Dermatitis Herpetiformis (DH)	Symmetrical grouped vesicular eruption elbows, knees, buttocks Intense pruritus	sulfone responsive	Anti-reticulin antibodies (10-25%)	Granular IgA in dermal papillae
Bullous Pemphigoid (BP)	Large tense bullae flexor surfaces of extremities, trunk and abdomen Oral lesions often present	May require prednisone	Anti-skin BMZ antibodies (usually IgG)	Linear IgG along BMZ (lamina lucida)

During the past five years several cases of linear IgA subepidermal bullous disease analogous to that described in adults have been identified in children. Most, if not all, of these children have had a clinical picture similar to that previously described as chronic bullous dermatosis of childhood (CBDC) (Prystowsky and Gilliam, 1976). This is a blistering disease of preschool children. The eruption is characterized by large, tense, clear or hemorrhagic bullae that arise from normal or inflammed skin. The bullae may form annular or rosette-like lesions composed of satellite blisters around a ruptured, crusted central lesion. Some patients have erythematous plaques with polycyclic margins bordered by intact bullae. The skin eruption tends to involve the lower trunk,

genital-crural regions, and lower extremities. Pruritus may be absent or intense. The course of this disease is characterized by periodic remissions with decreasing frequency of exacerbations usually with a complete remission within two to three years.

In the earlier descriptions of the immunopathology in these patients, basement membrane zone antibodies were not found. However, in these studies reagents for the detection of IgA were not used. In 1974, we identified a patient with linear BMZ IgA deposits with the clinical picture of chronic bullous diseases of childhood (Prystowsky and Gilliam, 1976). Since that time several additional children have been reported with similar clinical and immunopathologic findings (Chorzelski TB, et al., 1975).

The immunofluorescence findings in CBDC differ from those seen in patients with typical DH or BP. Although the linear BMZ pattern is similar to BP the predominant immunoglobulin class is IgA, not IgG. Circulating BMZ antibodies have been reported in only one case (van der Meer JB, et al., 1977). The incidence and severity of intestinal mucosal changes in CBDC are unknown and HLA studies have not been performed. Therefore, it is difficult to know whether this condition is an atypical form of DH or more closely associated with BP. However, for reasons mentioned above in the discussion of the adult form of linear IgA bullous dermatosis it seems reasonable at this point to consider CBDC, or linear IgA bullous dermatosis of childhood, as part of the spectrum of BP. Additional support for the concept that this represents a variant of pemphigoid comes from a recent paper by Jones and Goolamali (1980) entitled "IgA bullous pemphigoid: A distinct blistering disorder". Case I and Case II (see Appendix) are patients seen at this medical center with linear IgA subepidermal bullous disease.

Herpes Gestationis

Twelve years after herpes gestationis (HG) was separated from pemphigus by Milton in 1872, Duhring described the condition we now know as dermatitis herpetiformis. Duhring include HG as part of the spectrum of DH because: both conditions present with symptoms of intense itching and burning; both have vesiculobullous as well as inflammatory papular components; both are symmetrical in the arrangement of lesions, though this is less marked in HG; both share a tendency for lesions to appear in crops; and the vesicular lesions of both conditions may be in groups (i.e. herpetiform). The most obvious difference between DH and HG is that herpes gestationis is confined to women of child bearing age and occurs only during pregnancy or the immediate postpartum period. In contrast, DH occurs in either sex although more commonly in males and is not aggravated by hormonal fluctuations. Indeed, some cases have even disappeared completely during pregnancy and returned after delivery. In spite of these clinical differences DH herpetiformis was not clearly separated from HG until the discovery less than 15 years ago of the distinctive immunopathological changes in each condition.

Clinical Features of HG

The eruption of HG usually begins with a patch of erythema in a single area around the umbilicus or on a forearm; from this point it steadily extends to other areas. Blisters eventually appear and the sensations of itching and burning progressively intensify until they become almost unbearable. The clinical appearance at the height of the eruption closely resembles BP. In some cases erythematous annular and target-like lesions simulate EM. In contrast to the centrally located bullae in EM, the blisters in HG are more often arranged around the periphery of the erythematous plaques and may arise on normal skin. In addition, EM is an acute self-limiting disease lasting three to four weeks whereas HG will persist to the end of pregnancy.

Pathology and Immunopathology of HG

Although clinical confusion between BP, DH and EM may occur, the histologic and especially the immunopathologic features are quite distinctive (Hertz, et al., 1976). Nonblistered urticaria-like lesions show a mixed lymphocytic, histiocytic and eosinophilic infiltrate about small dermal blood vessels, marked edema of the papillary dermis with necrosis of overlying basal cells and focal spongiosis. The early blisters form as a result of basal cell necrosis similar to that seen in the epidermal variety of EM. The absence of polymorphonuclear leukocytes in the early lesions of HG is distinctly unlike the early changes of DH and the blisters in HG occur above the dermal papillae. On the other hand, differentiation from the "cell rich" form of BP may be difficult if not impossible.

Provost and Tomasi (1973) first discovered C3 and properdin localized to the BMZ of skin from two patients with HG. The following year Bushkell and coworkers (1974) demonstrated IgG, C1q, and C3 at the BMZ and circulating IgG anti-BMZ antibodies similar to those seen in patients with BP. These observations have been confirmed by several investigators and it is now well established that patients with HG have circulating IgG antibodies which fix complement to the lamina lucida area of the epidermal BMZ as shown in Figure 10 (Yaoita, et al., 1976A).

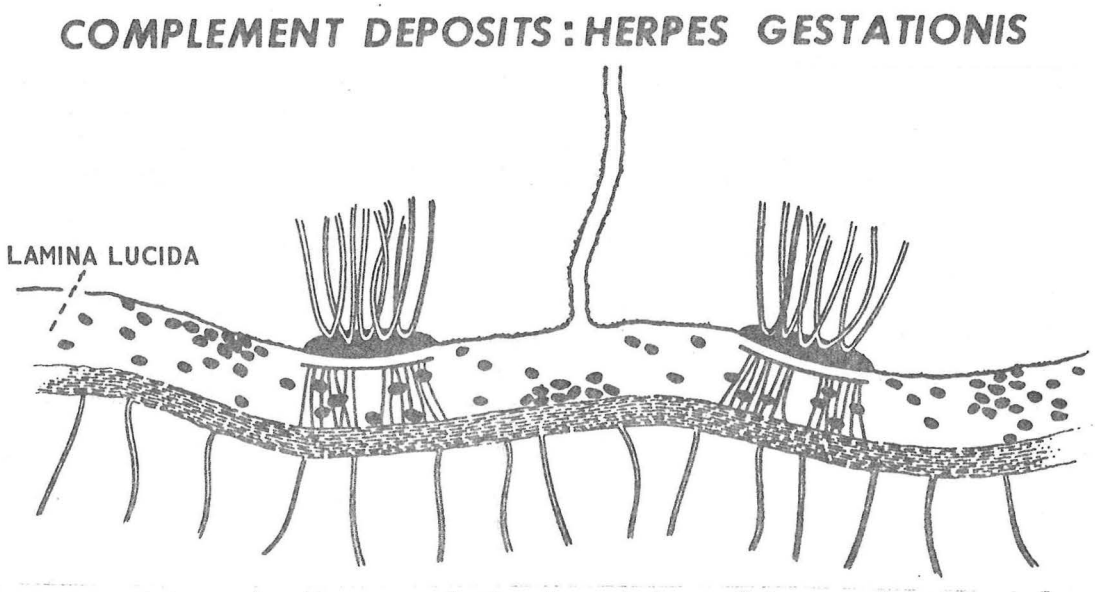

Figure 10. Schematic diagram of the deposition of immunoglobulin and complement in herpes gestationis.

Several reports have indicated that infants born of mothers with HG may have urticarial, vesicular or bullous skin lesions at birth and briefly during the neonatal period (Chorzelski , et al., 1976)(Katz, et al., 1976). The lesions in the infant resolve spontaneously within the first several days after delivery. An example of this is described in the Appendix, Case III.

Immunopathologic studies in these affected children have demonstrated complement bound to the BMZ and circulating anti-BMZ antibody. The brief time course of the disease in the newborn suggest that the lesions resolve with the disappearance of maternal hormones. Thus, the expression of HG seems to depend upon the presence of complement fixing IgG anti-BMZ antibodies (to lamina lucida) and certain undefined pregnancy related factors. It seems likely that these factors act by augmenting an inflammatory effector system that is focused and triggered by the complement fixing anti-BMZ antibody.

Proposed Pathogenesis of Pemphigoid

The presence of bound and circulating complement-fixing IgG antibodies in patients with BP has now been well established (Jordon, et al., 1967). Pemphigoid antibody has been found to activate complement in normal serum in the presence of a BMZ antigen supplied by skin slices in vitro (Jordon, et al., 1969 and 1978). Deposition of both classical and alternative complement pathway proteins have been demonstrated in the BMZ. Furthermore, in pemphigoid patients blister fluid complement levels are reduced (Jordon, et al., 1973) and the blister fluid contains a neutrophil chemotactic factor cleaved from the fifth component of complement (Diaz-Perez JL and Jordon RE, 1976). Therefore, pemphigoid clearly appears to be a disease in which complement activation plays a primary role. This also seems to be the case in HG. Organ culture of normal skin grown in the presence of pemphigoid antibody with or without the presence of complement shows no pathologic change even though antibody and complement bind in the lamina lucida region of the BMZ. Such studies demonstrate the need for effector mechanisms (either cellular or humoral) that are not present in the organ culture system (Pehamberger, et al., 1980).

Dermatopathologists have long recognized that eosinophils are prominent in the inflammatory infiltrate of BP (Lever, 1975)(Freeman RG, 1980). The peribullous area often shows eosinophils in the upper dermis in close approximation to the epidermis frequently lined-up beneath the BMZ (van der Meer, as quoted by Lever, 1975). Figure 11 demonstrates this localization of eosiniphils along the BMZ (Ackerman, 1978). The presence of a low molecular weight eosinophil chemotactic factor in bullous fluids of pemphigoid patients and recent histologic evidence of mast cell migration into the upper dermis followed by degranulation in early BP lesions suggests that mast cell derived factors (e.g. ECF-A, histamine) may be important in triggering the early pathologic events (Baba, et al., 1976)(Wintroub, et al., 1978). This would account for the presence of large numbers of eosinophils in these lesions.

Recent studies have clearly demonstrated that eosinophils are efficient killer cells in certain parasitic diseases (Sullivan TJ, 1979). Anwar and Kay (1977)(1978) have shown that the mast cell products,

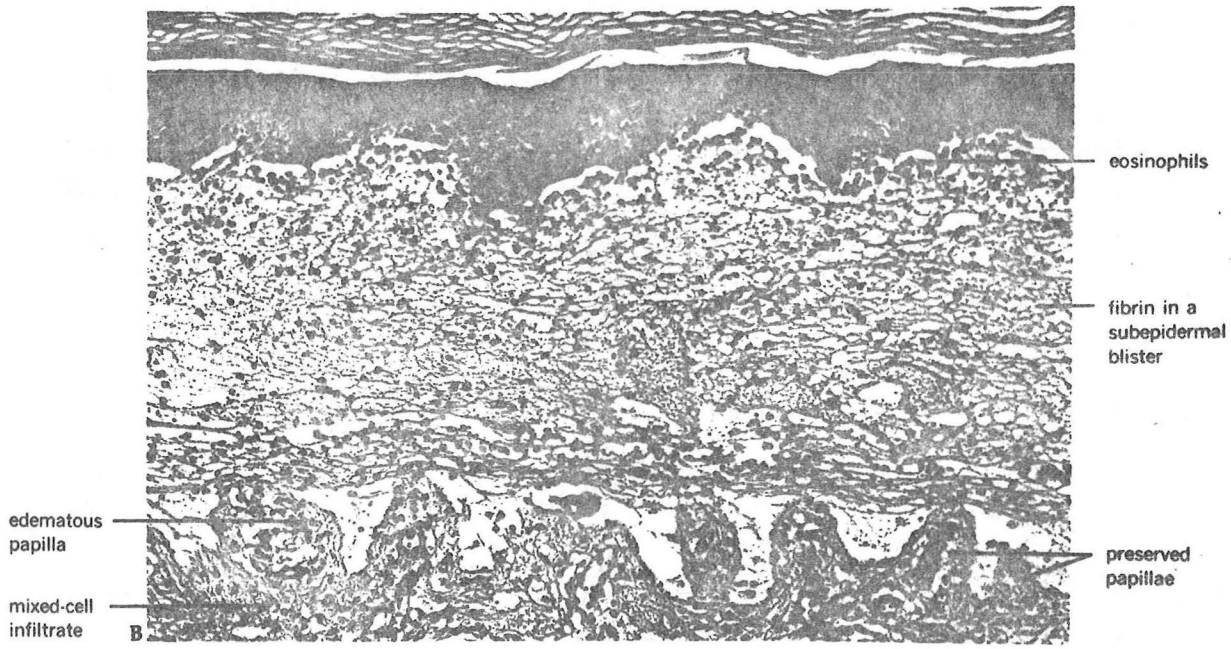

FIG. 11 Pemphigoid, cell-rich type. A, Diagnostic features pictured are subepidermal vesiculation, preservation of dermal papillae, and perivascular and interstitial infiltrate replete with eosinophils. (× 45.) B, As illustrated in this higher magnification pemphigoid usually can be differentiated from dermatitis herpetiformis because there are more eosinophils than neutrophils within papillary dermis and blister and dermal papillae tend to line up like tombstones, an appearance sometimes referred to as festooning. (× 169.)

eosinophil chemotactic factor of anaphylaxis (ECF-A) and histamine, are not only chemotactic for eosinophils but also selectively increase the number of complement receptors on the surface of eosinophils and the percentage of eosinophils expressing C3b receptors (Kay, et al., 1980).

Several well-defined mechanisms whereby eosinophils can effectively kill parasites and produce tissue injury have been pointed-out (Sullivan TJ, 1979). Eosinophils binding to nonphagocytosable surfaces via either complement or IgG receptors have been shown to release granular contents leading to damaging effects on target membranes. The exact mechanisms of injury are not known; however, superoxide, singlet oxygen or hydroxyl radical formation have been suggested as possible effector mechanisms since an oxidative burst is known to occur at least during phagocytosis. Although eosinophils are now clearly implicated in host defense against parasitic invasion, there is little evidence to date identifying these cells as the principal cell type in the production of tissue injury in any disease state. The circumstantial evidence cited above suggests

that eosinophils recruited and armed by the products of dermal mast cells may be focused and triggered by binding via cell surface C3b receptors to complement along the epidermal basement membrane thus producing injury localized to this site. This mechanism is outlined diagrammatically below (Figure 12).

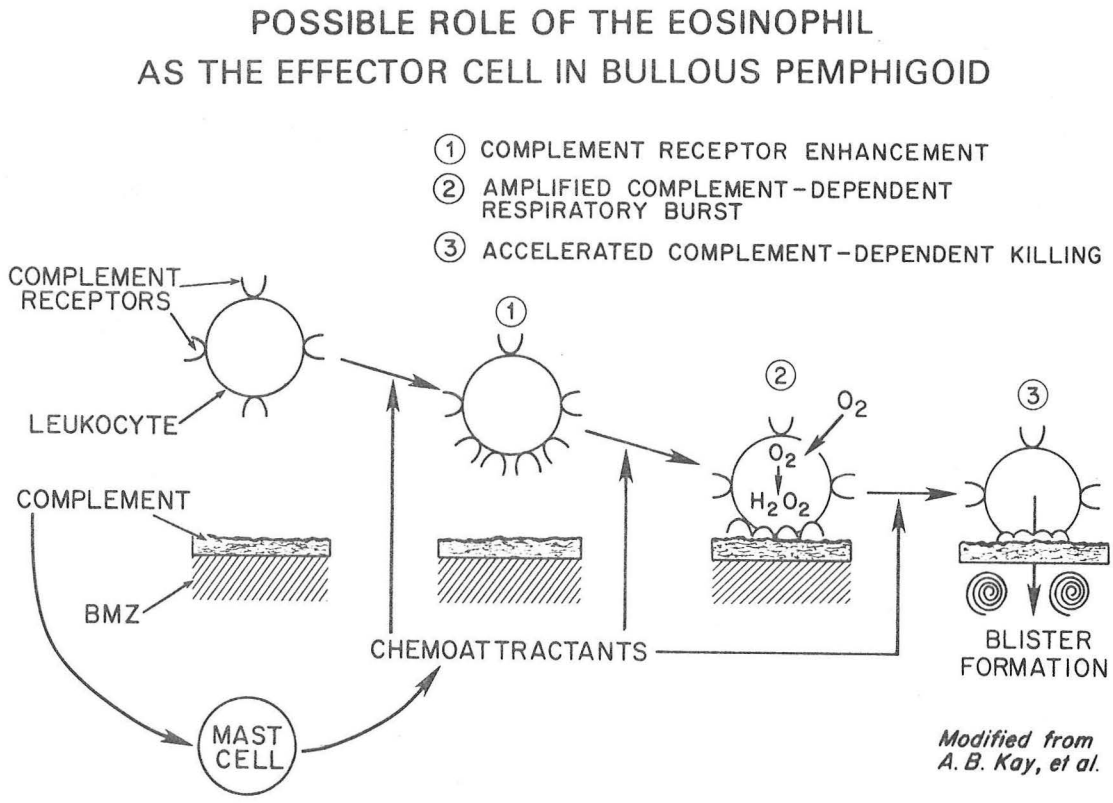

Figure 12. Anaphylatoxins (C3a, C5a) and/or antigen may trigger dermal mast cells to release factors (SRS-A, histamine, etc.) which attract eosinophils and enhance their complement (C3b) receptors (Anwar and Kay, 1978)(Wintroub, et al., 1978). These C3b bearing eosinophils may then bind to the complement fixed by anti-BMZ antibody to the BMZ producing local injury and dermal epidermal separation.
(Anwar ARE and Kay AB: J Immunol 121:1245, 1978; Wintroub BU, et al.: N Eng J Med 298:417, 1978; Sullivan TJ: Prog Hematol 11:65, 1979; and Nieboer C and van Leewen JE: Arch Dermatol 116:555, 1980)

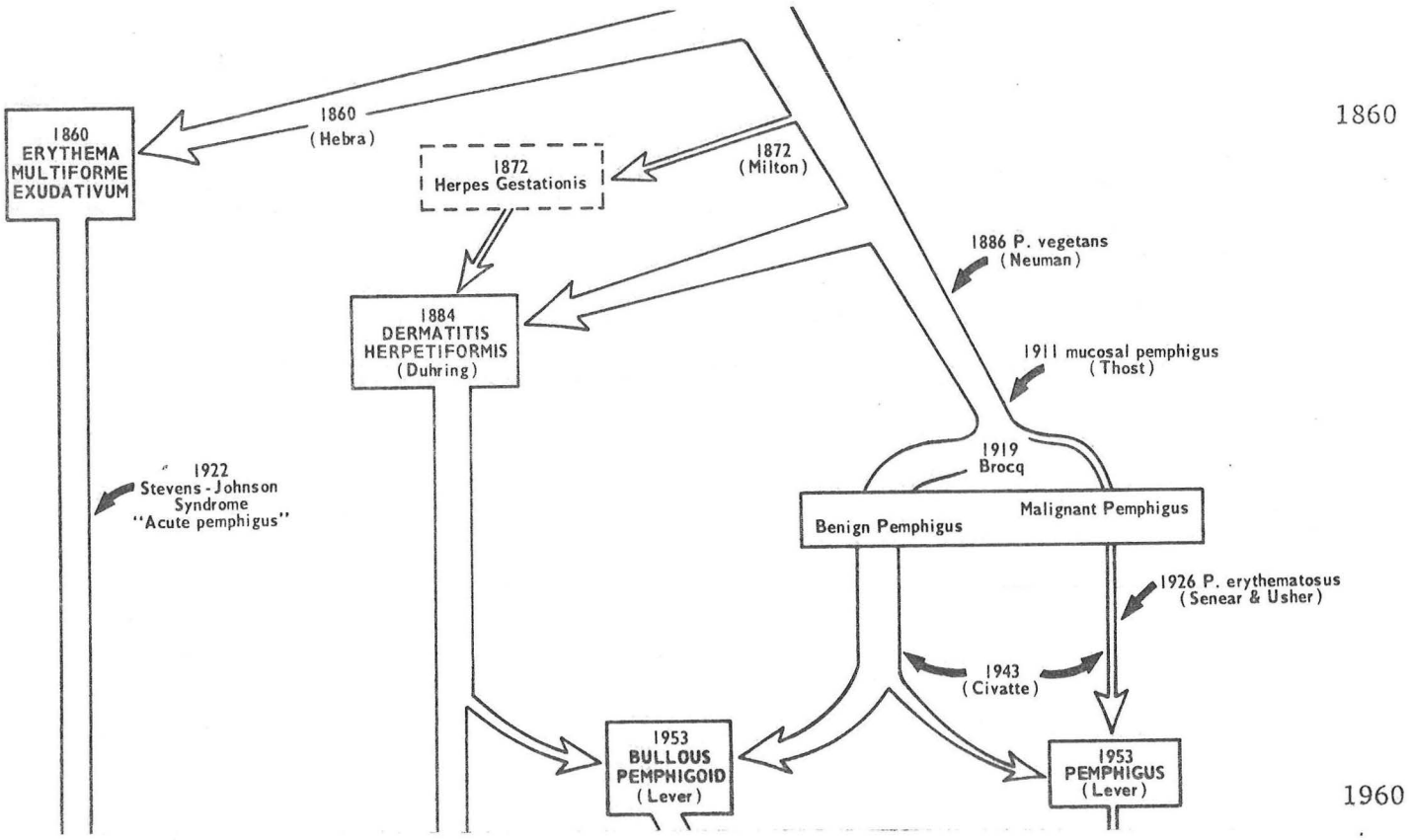

Figure 13.

PEMPHIGUS GROUP

The definition of pemphigus as a distinct clinical and histopathological entity developed during the 100 years between 1860 and 1960 (see Figure 13). During that time other chronic bullous diseases were recognized and separated from pemphigus ultimately leaving a relatively small homogeneous group. During the past thirty years the clinical status of pemphigus has changed from a disease with a five year fatality rate of

greater than 90% to less than 30% (See Figure 14). This improvement in survival followed the introduction of high dose steroids in the management of this condition. Other factors such as earlier diagnosis, improvement in the control of infections and better management of metabolic disturbances which frequently complicate this disorder or its treatment are also important. In the past 10 to 15 years the use of "immunosuppressive" agents have reduced some of the steroid related complications. The most remarkable progress in our understanding of the pathogenesis of pemphigus and related chronic blistering diseases followed the discovery by Jordon and Beutner in 1964 that pemphigus patients have antibodies that bind to the epidermis.

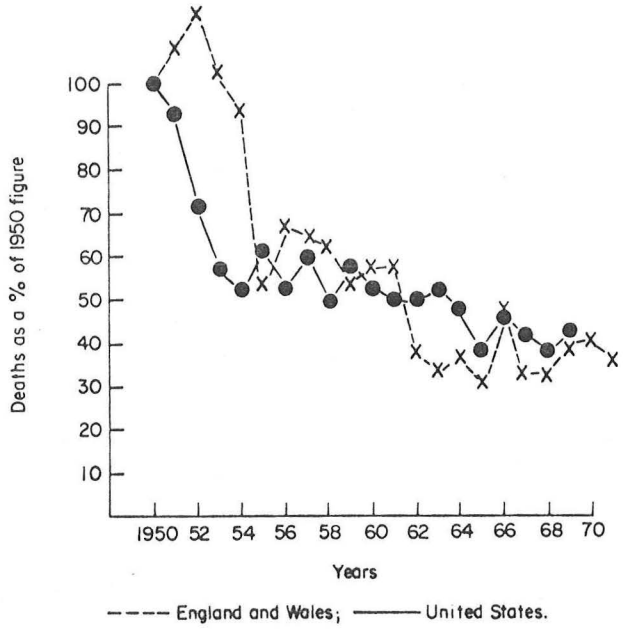

Figure 14. Deaths from bullous diseases in the United States, and in England and Wales from 1950 to 1972. Figures calculated as a percentage of the 1950 figure.
(Savin JA: International mortality from bullous diseases since 1950. Brit J Dermatol 94:149, 1976)

Clinical Features of Pemphigus Vulgaris

Pemphigus is a disease of middle-aged people occurring most frequently between the ages of 40 and 60 years (See Figure 6). The incidence is approximately equal for the two sexes but there is a predominance for Jewish persons in all series varying between 25 and 75%. Southern

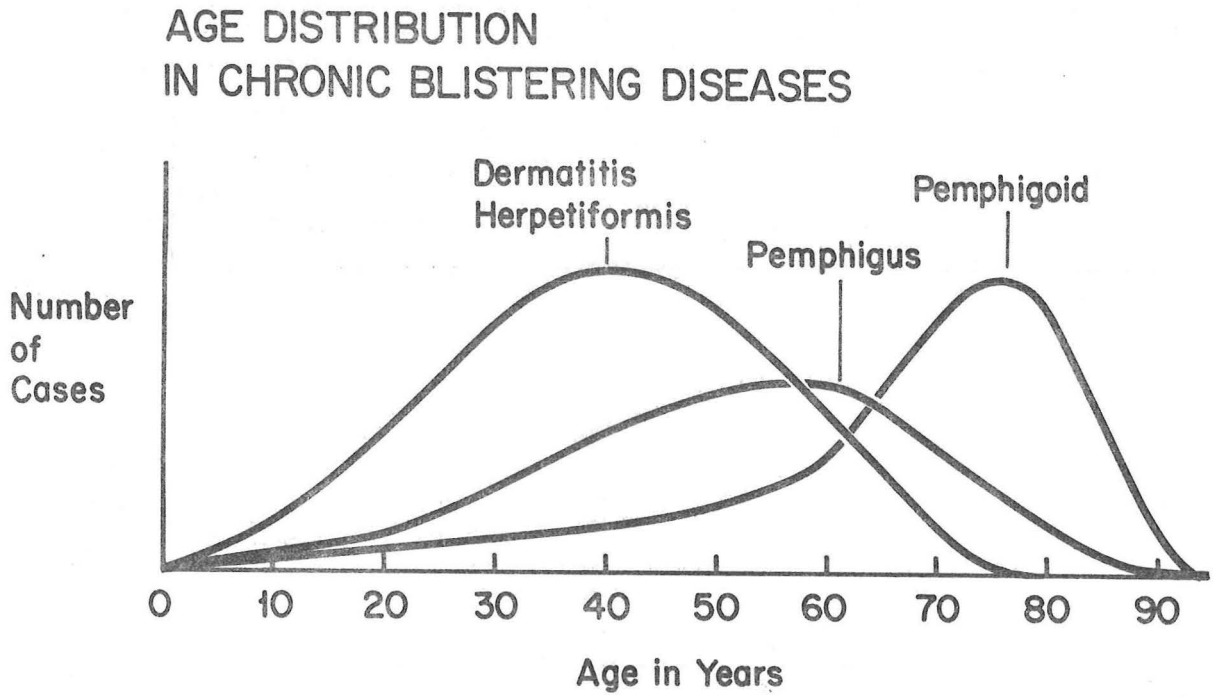

Figure 6.

European and Mediterranean people seem to be more prone to the disease than Northern Europeans, which is opposite to DH. As shown below, there are two major types of pemphigus recognized by differences in clinical appearance and site of involvement in the epidermis. These are pemphigus vulgaris and pemphigus foliaceus. Pemphigus vegetans is a variant of pemphigus vulgaris while pemphigus erythematosus is a variant of pemphigus foliaceus.

CLASSIFICATION OF PEMPHIGUS

Pemphigus Vulgaris

Pemphigus Vegetans

Pemphigus Foliaceus

Pemphigus Erythematosus

The disease usually begins in a localized fashion and oral lesions are the presenting manifestations in over 60% of the patients. Painful oral erosions or a patch of weeping, crusted or often purulent "eczema" may be present on the scalp or face for weeks or even months before a generalized bullous eruption appears. Bullae generally arise on normal, uninflammd skin. Because of their intraepidermal origin the bullae are fragile and quickly rupture giving rise to painful superficial erosions. The erosions have a characteristic tendency to enlarge peripherally and heal slowly if at all. Tags of epidermis are present at their margins where separation between the epidermal layers continues. Itching is mild or absent, but pain is frequently severe. Nikolsky's sign is always found in pemphigus when skin lesions are present. This sign is elicited by placing the finger gently but firmly on an area of normal skin close to a lesion and pushing sideways. If the sign is present the finger will cause the upper layers of the epidermis to slide over the layers below, producing the appearance of a flaccid bulla without fluid contents. This sign can also be elicited on inflamed skin in other bullous diseases such as pemphigoid, severe erythema multiforme, or toxic epidermal necrolysis.

Mucosal involvement occurs in pemphigus vulgaris in almost all cases. Lesions can be confined to the oral mucosa causing considerable pain and discomfort when eating. This often leads to significant weight loss. The lips, buccal mucosa and gums are the common sites but any region of the oral or pharangeal cavities may be affected.

The clinical course in untreated patients is usually slow and prolonged with steady inexorable spread eventually leading to death after a period of one to two years. Case IV (see Appendix) illustrates the magnitude of this problem when unrecognized and treatment is delayed.

Clinical Features of Pemphigus Vegetans

This variant of pemphigus vulgaris is thought to develop in patients that have an increased resistance to the disease. It may be seen as part of more typical pemphigus vulgaris, or seemingly as an independent process. For example, patients with pemphigus vulgaris may develop pemphigus vegetans-like lesions as their condition is coming under control with corticosteroid therapy. When it arises de novo pemphigus vegetans generally starts at an earlier age. Oral lesions are common in both, but in pemphigus vegetans heaped-up vegetating lesions form on the margins of the lips and rarely inside the mouth. Other mucosal surfaces, particularly the vulva and anus are often affected. In early stages blisters identical with those of pemphigus vulgaris appear but the denuded erosions that follow develop hypertrophic granulations at their edges. The vegetations exude serum or pus and are often studded with small pustules. Frequently fresh blisters form at the edge of the vegetations which in turn give rise to new vegetations. These vegetations become dry, heaped-up, hyperkeratotic and eventually fissured. Lesions may occur on any part of the body but are more often seen in the flexural areas.

Occasionally patients with pemphigus vegetans undergo spontaneous remission, however, in most cases the disease is prolonged and in some cases may eventually be fatal. Case V, in the Appendix, is a patient seen at Parkland with Pemphigus Vegetans.

Clinical Features of Pemphigus Foliaceus

The age of onset in pemphigus foliaceus varies widely and the syndrome can occur in children. The onset is usually slow with the appearance of a few lesions on the face or scalp, upper chest and back. Flaccid bullae may appear but more often the patient presents with scaling and crusting similar to severe (or infected) seborrheic dermatitis. The lesions may assume a butterfly distribution on the face with an erythematous scaly appearance which may simulate lupus erythematosus. In widespread cases the whole body surface becomes involved in an erythroderma with scaling and crusting, oozing and weeping. At this stage the appearance is that of an exfoliative dermatitis. Oral mucous membrane involvement is unusual and if present often superficial and relatively asymptomatic. Occasionally patients with pemphigus foliaceus may present with serpiginous lesions with small vesicular lesions at the margins resembling dermatitis herpetiformis. In the past this morphologic variety produced confusion leading some to consider a tranformation of dermatitis herpetiformis into pemphigus foliceus. Using current histo- and immunopathologic techniques the identification and classification of these unusal morphologic forms has been greatly simplified. The concept of an "intermediate bullous disease" in patients with features of both pemphigus and dermatitis herpetiformis has recently been reviewed by Knight and coworkers (1976). They describe nine patients all of whom showed eosinophilic spongiosis and six with intercellular epidermal antibodies, well recognized features of pemphigus. Similar patients have been reported as examples of "mixed bullous disease" (Barranco, 1975), "acantholytic dermatitis herpetiformis" (DeMento FJ and Grover RW, 1973), and "herpetiform pemphigus" (Jablonska S, et al., 1975). All of these patients had eosinophilic spongiosis and positive pemphigus antibodies. Thus, the current view is that most if not all patients with this overlapping clinical picture are suffering from an atypical form of pemphigus foliaceus. The importance of recognizing this type of pemphigus foliaceus is that unlike other forms it appears to respond to sulfones either alone or in combination with low doses of prednisone.

In general, patients with pemphigus foliaceus have a relatively benign chronic condition requiring less aggressive therapy than pemphigus vulgaris. Case VII in the appendix has probably had pemphigus foliaceus for over 20 years and has never received systemic steroids.

Other variants of pemphigus have been described. Fogo salvagem is a variety of pemphigus foliaceus which is endemic in a certain area of Brazil (Viera, 1940). A form of pemphigus has also been described in India which occurs very frequently in children and adolescents. Whether these endemic forms stem from a peculiar environmental agent or unique genetic factors is unknown.

Pemphigus Erythematosus

Pemphigus erythematosus, originally described by Senear and Usher in 1926 as a variety of pemphigus with clinical features of lupus, has been considered to be a localized variety of pemphigus foliaceus. However, in recent times evidence for more than a simple clinical resemblance to lupus erythematosus has developed. In addition to the

finding of immunoglobulin bound in the intercellular cement substance (ICS) of the epidermis recent studies have shown that patients with pemphigus erythematosus frequently have immunoglobulin (or immune complexes) deposited at the dermal epidermal junction, a characteristic finding of lupus erythematosus. In addition, such patients have been found to have antinuclear antibodies and a few cases have had well documented cutaneous or systemic lupus erythematosus. Case VIII (see Appendix) has both pemphigus erythematosus and subacute cutaneous LE.

Histopathology and Immunopathology of Pemphigus

The principal abnormality in all varieties of pemphigus is separation of epidermal cells, a process known as acantholysis. The earliest change in pemphigus vulgaris consists of edema between and above the basal cells of the epidermis followed by the formation of a cleft in the suprabasalar region. In pemphigus vulgaris the blister roof is formed by the greater part of the epidermis which has a ragged lower surface formed by loosely adherent epidermal cells. The floor of the blister is composed of basal cells which remain attached to the dermis. Early lesions are usually devoid of inflammatory cells but later a mixture of eosinophils, polymorphonuclear leukocytes and lymphocytes appear.

In pemphigus vegetans the early lesions are the same as pemphigus vulgaris, i.e. acantholysis with the formation of a suprabasalar blister. In time there is downward growth of thick strands of epidermal cells into the dermis and intraepidermal collections of eosinophils (eosinophilic spongiosis).

The earliest histologic changes in pemphigus foliaceus and pemphigus erythematosus are in the upper layers of the epidermis. Cells in the granular layer separate by acantholysis to form a subcorneal blister. Older lesions show more prominent acantholysis, hyperkeratosis and parakeratosis. Dyskeratotic cells occur frequently and when present in the superficial layers of the skin may resemble the grains of Darier's Disease. Recent findings by Bystryn and coworkers using immunofluorescence techniques have shown that the anti-ICS antibody tends to localize in a more superficial portion of the epidermis in patients with pemphigus foliaceus. These workers have presented evidence that the superficial localization of the antibody is not due to a difference in the antibody specificity but more likely the result of an absence of the "pemphigus antigen" in the ICS of the lower portion of the epidermis of pemphigus foliaceus patients' skin (see Pathogenesis below).

Electron microscopic studies have shown an early dissolution of the interepidermal cement substance (ICS) causing widening of the intercellular spaces and loss of desmosomal attachments. Retraction of the epidermal cytoplasmic tonofilaments and disappearance of the desmosomes occurs as a secondary phenomenon and is the final stage leading to loss of epidermal cell cohesion.

Direct immunofluorescence studies show antibody (IgG) bound to the epidermal ICS (see Figure 15). This is best demonstrated in skin next to a bullous lesion or in normal appearing skin. Complement components are only found in active acantholytic areas at the margin of the bullous cavity and complement fixation by pemphigus antibody in vitro using normal skin or other stratified epithelial substrates has not been possible (Jordon, 1968).

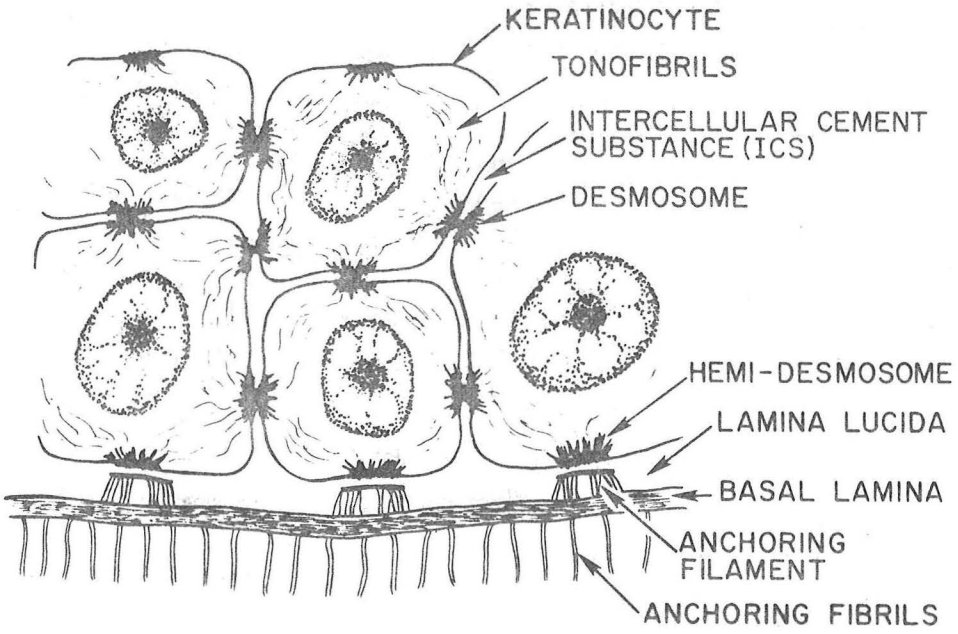

Figure 15. Schematic diagram of the intercellular structure of the epidermis. Pemphigus antibody binds to the intercellular cement substance (ICS) leading to loss of cellular adherence or acantholysis. The basal keratinocytes maintain their attachment to the basal lamina by hemi-desmosomes and attachment proteins (e.g. laminin, etc.) in the lamina lucida so that a suprabasalar bulla develops.

Proposed Pathogenesis of Pemphigus

To summarize, pemphigus is a severe intraepidermal blistering disease with autoimmune features limited to the skin and mucous membranes. These patients produce an IgG antibody that is specific for an antigen in the intercellular cement substance (ICS) of the epidermis. Binding of this antibody results in loss of the normal adhesive forces between epidermal cells (keratinocytes), a process that has been termed acantholysis. As mentioned there are two major clinical types of pemphigus which are differentiated histologically by the level of acantholysis in the epidermis. Pemphigus vulgaris arises deep in the epidermis just above the basal cell layer (suprabasalar). Pemphigus foliaceus lesions develop high in the epidermis resulting in a fragile more superficial (subcorneal) blister.

It has been suggested that acantholysis in pemphigus is a manifestation of cytotoxic injury from complement dependent mechanisms since complement components are frequently present in the bullous lesions. Even though bullous fluid complement levels are reduced (Jordon, 1973B) and complement components are often bound to the cell surfaces of acantholytic cells, the failure to demonstrate complement fixation by pemphigus antibody in vitro and the absence of complement components bound with antibody to the ICS in uninvolved skin cast doubt on the importance of complement as a primary factor in the genesis of acantholysis.

A series of recent observations have suggested that pemphigus antibody mediated acantholysis can occur completely independent of complement activation and in fact may represent a previously undescribed mechanism of antibody mediated cellular injury. In 1974, Michel and Ko reported that epidermal acantholysis could be produced in human skin explants in the presence of whole pemphigus (vulgaris or foliaceus) serum (Michel and Ko, 1974; 1977). The same changes were produced when the pemphigus serum had been heat inactivated at 56°C for 30 minutes. Schiltz has pointed out that two Italian workers published similar observations in 1956 (Bellone and Leone, 1956); however, the significance of their work seems to have been overlooked. Schiltz and Michel (1976) showed that it was the IgG fraction of pemphigus sera that produced these in vitro acantholytic changes and further confirmed that complement was not necessary for this reaction. These observations were later confirmed by other groups using both human (Ruocco, et al., 1978) and monkey skin (Deng, et al., 1977). Schiltz, et al. (1978) then demonstrated that when suspensions of human epidermal cells were incubated with pemphigus IgG a series of changes occurred which resulted in death of the epidermal cells. These changes appeared to be mediated by a nonlysosomal proteolytic enzyme produced by, or released from, epidermal cells in response to pemphigus antibody binding to their surfaces (Schiltz, et al., 1978). In the same year Farb, et al. (1978) reported that the addition of pemphigus serum to mouse epidermal cell monolayer cultures led to antibody binding to the cells and a reduction of cellular adherence to the culture vessel. They demonstrated that this loss of adherence was blocked by serine protease inhibitors and alpha-2 macroglobulin suggesting that pemphigus acantholysis may result from the release or generation of a neutral serine proteinase. Schiltz, et al. (1979) have further characterized this enzyme which they have designated the "pemphigus acantholysis factor". Using human skin explant cultures they have shown that a heat-labile proteolytic enzyme is either synthesized or activated from a precursor in viable epidermal cells in response to cell surface binding by pemphigus IgG antibody.

The discovery of a noncomplement antibody-dependent system which may be capable of inducing human disease in the absence of inflammatory cells is an important biologic observation whose significance obviously extends far beyond the field of dermatology. These exciting findings could lead to a new therapeutic approach to pemphigus. It would be of interest to know if any of the potent serine proteinase inhibitors that are presently available would be beneficial in patients with this disease.

Associated Conditions

Thymoma and Myasthenia Gravis

Pemphigus has been relatively frequently reported with thymoma and/or myasthenia gravis. Table IX lists fifteen cases of coexistent pemphigus and thymoma from the literature. The pemphigus was unaffected by thymectomy in these cases. Myasthenia gravis occurred in ten of the fifteen cases. Thus, pemphigus and thymoma seem to be associated,

TABLE IX

Pemphigus and thymoma

Author	Type of pemphigus	Type of thymoma	Interval between thymoma and pemphigus*	Presence of myasthenia gravis
Kough and Barnes	Vulgaris	Benign	−27 months	−
Peck et al	Vulgaris	Malignant	Unknown	+
Beutner et al	Erythematosus	Unknown	1 month	+
Beutner et al	Erythematosus	Unknown	−60 months	+
Jablonska et al	Erythematosus	Unknown	Unknown	+
Stillman and Baer	Vulgaris	Benign	−6 months	−
Krain and Bierman	Vulgaris	Unknown	Unknown	−
Vetters et al	Vulgaris	Benign	−9 months	+
Noguchi and Nishitani	Vulgaris	Benign	8 months	+
Hausmanowa-Petrusewicz et al	Erythematosus	Benign	3 months	+
Kavli	Vulgaris	Benign	Concurrent	−
Safai et al	Vulgaris	Benign	32 months	+
Bryon	Erythematosus	Benign	−96 months	+
Imamura et al	Foliaceus	Benign (spindle cell)	−48 months	+
Uhlin et al	Erythematosus	Benign	−36 months	−

*− indicates that pemphigus appeared first.

(Kough RH, Barnes WT: Ann Intern Med 61:308, 1964; Peck SM, Osserman KE, Weiner LB, et al.: N Engl J Med 279:951, 1968; Beutner EH, Chorzelski TP, Hale WZ, et al.: JAMA 203:845, 1968; Jablonska S, Chorzelski TP, Leboida J: Hatarzt 21:156, 1970; Stillman MA, Baer RL: Acta Derm Venereol (Stockh) 52:393, 1972; Krain LS, Bierman SM: Cancer 33:1091, 1974; Vetters JM, Saikia NK, Wood J, et al.: Brit J Dermatol 88:437, 1973; Noguchi S, Nishitani H: Neurology 26:1075, 1976; Hausmanowa-Petruesewicz I, Chorzelski T, Strugalska H: J Neurol Sci 9:273, 1969; Kavli G: Brit J Dermatol 99:97, 1978; Safai B, Gupta S, Good RA: Clin Exp Dermatol 3:129, 1978; Bryon WA: Case presentation at Cincinnati Derm Society, 11/7/79; Imamura S, Takigawa M, Ikai K, et al.: Clin Exp Dermatol 3:285, 1978; Uhlin SR, Maiocco KJ, Bhatia SG: Cutis 25:177, 1980)

however, there appears to be little or no direct relationship between the two disorders. Table X reviews the data suggesting an association between pemphigus and myasthenia gravis. A total of 19 cases have been reported with both conditions. All forms of pemphigus have been seen with myasthenia and only half the patients had a thymoma. Notice that in three cases other "autoimmune" conditions have occurred (two with lupus erythematosus and one with red cell aplasia).

TABLE X

Association of pemphigus and myasthenia gravis

Type of pemphigus	No.	No. with thymoma	No. that are concurrent	Other diagnosis
Vulgaris	9	4	0	—
Erythematosus	7	5	1	Lupus erythematosus (2 cases)
Foliaceus	2	1	0	Red cell aplasia (1 case)
Unknown	1	0	0	—
Total	19	10	1	

(Callen JP: J Am Acad Derm 3:107, 1980)

Malignancy

Table XI summarizes the reported cases of pemphigus and malignancy. Twenty-three cases have been reported; sixteen with solid tumors and seven with tumors involving the reticuloendothelial system. The type of pemphigus and the types of tumors vary widely. A patient has been described with an "epidermoid" squamous cell carcinoma on the leg which was discovered after the diagnosis of pemphigus vulgaris was made. When this tumor was removed the pemphigus resolved (Saikiak, 1972). These data are impossible to analyze statistically, and it is doubtful that malignancy is more common in pemphigus than in age matched controls.

TABLE XI

Pemphigus and malignancy

Author	Type of pemphigus	Type and site of malignancy	Months from malignancy to pemphigus*
Solid tumors			
1. Krain	Vulgaris	Breast-scirrhous	+1
2. Krain	Vulgaris	Breast-scirrhous	−20
3. Krain	Vulgaris	Endometrium	−12
4. Krain	Vulgaris	Bladder-squamous cell	−12
5. Sheckalov	Vulgaris	Esophagus	Concurrent
6. Ryan	Vulgaris	Ovary	+Unknown
7. Lever	Vulgaris	Stomach	−Unknown
8. Jacobs et al	Vulgaris	Breast-medullary adenocarcinoma	+2-3 months
9. Chang et al	Vulgaris	Epidermoid (skin, leg)	Concurrent†
10. Saikia et al	Erythematosus	Lung	−15
11. Saikia et al	Erythematosus	Bronchus-adenocarcinoma	+13
12. Saikia et al	Erythematosus	Lip, possibly metastatic to liver	+198
13. Rosenberg et al	Unknown	Colon-adenocarcinoma	Unknown
14. Rosenberg et al	Unknown	Colon-adenocarcinoma	Unknown
15. Rosenberg et al	Unknown	Pancreas-adenocarcinoma	Unknown
16. Rosenberg et al	Unknown	Breast-adenocarcinoma	Unknown
Reticuloendothelial tumors			
17. Peck et al	Vulgaris	Thymoma (malignant)	Unknown
18. Saikia	Vulgaris	Giant follicular lymphoma	+1
19. Baird	Vulgaris	Lymphoblastoma	+12
20. Muller et al	Vulgaris	Lymphosarcoma	+12
21. Pisanty and Garfunkel	Vulgaris	Kaposi's sarcoma	+20
22. Rosenmann	Vulgaris	Kaposi's sarcoma	−3
23. Katz et al	Vulgaris	Histiocytic lymphoma	−33

*− indicates that the pemphigus developed first; + indicates that the malignancy occurred first.

†Pemphigus resolved when tumor was removed.

(Krain LS: Brit J Dermatol 90:397, 1974; Sheckalov ND: Sov Med 29:122, 1966; Ryan JG: Arch Dermatol 104:14, 1971; Jacobs R, Eng AM, Solomon LM: Int J Dermatol 17:221, 1978; Chang CM, et al., as quoted by Saikia NK: Brit J Dermatol 88:407, 1973; Saikia NK, MacConnell LES: Brit J Dermatol 87:1, 1972; Rosenberg FR, Sanders S, Nelson CT: Arch Dermatol 112:962, 1976; Peck SM, Osserman KE, Weiner LB, et al.: N Engl J Med 279:951, 1968; Saikia NK: Brit J Dermatol 86:411, 1972; Baird PC: N Engl J Med 214:211, 1936; Muller SA, Hermann ED, Winkelmann RK: Am J Med 52:102, 1972; Pisanty S, Garfunkel A: J Oral Med 25:89, 1970; Rosenmann E: Isr J Med Sci 2:269, 1966; Katz AL, Nashel DJ, Goard CP, et al.: South Med J 72:1463, 1979)

Autoimmunity

Pemphigus has been reported in patients with various other disorders presumably of an autoimmune nature. Sporatic but well documented reports of patients with pemphigus and pernicious anemia (Mackie, 1973), red cell aplasia (Imamura, 1978), lupus erythematosus (Chorzelski, 1968), rheumatoid arthritis (Falk, 1979), autoimmune thyroiditis (Diaz, 1980), Sjogren's syndrome (Chorzelski, 1974), bullous pemphigoid (Beutner, 1970) and lymphomatoid granulomatosis (Jauregui, 1978) have appeared.

HLA-DR4 has been found in 91% of Jewish pemphigus patients (Park MS, 1979), in 70% of patients with rheumatoid arthritis (Stastny P, 1978) and in 73% with hydralizine-induced SLE (Batchelor JR, 1980). These findings suggest the possibility that HLA-DR4 is genetically linked to some controlling function of the immune response which predisposes to certain types of autoreactivity.

Penicillamine Induced Pemphigus

Degos and coworkers first reported the occurrence of penicillamine induced pemphigus vulgaris in a patient with Wilson's Disease in 1969 (cited by Lever, 1979). Since then over 30 cases have been reported. Most of the cases of penicillamine induced pemphigus have been of the foliaceus type and in most patients it appeared between six and twelve months after institution of treatment. The pemphigus usually subsided spontaneously after withdrawal of penicillamine. In one case pemphigus foliaceus has ended fatally (Sparrow, 1978). Direct immunofluorescence and histopathologic findings have been diagnostic of pemphigus in all cases examined.

A single case of pemphigus probably induced by penicillin has been reported by Ruocco and coworkers (1979). These authors suggested that the disease was due to penicillamine formed by the metabolic breakdown of the penicillin molecule.

CONCLUSION

From the 1790's to the 1970's our concept of Pemphigus evolved from a single ill-defined chronic blistering process into a number of distinct sharply focused autoimmune skin diseases. Recent advances in our understanding of immunopathologic mechanisms of injury may well lead to better management of these devastating diseases in the 1980's.

ACKNOWLEDGMENT

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TABLE XII

IMMUNOFLUORESCENCE FINDINGS IN VESICULOBULLOUS DISEASES

Disorder	% pos. DIF*	Binding site	Principal Immunoreactants	% pos. IFF**
Pemphigus	80-95%	Intercellular substance	IgG	75-90%
Bullous Pemphigoid	∿100%	BMZ	IgG & C3	70%
Cicatricial Pemphigoid	65-85%	BMZ	IgG & C3	uncommon
Herpes Gestationis	∿100%	BMZ	C3 (rarely IgG)	rare
Dermatitis Herpetiformis	∿100%	papillary dermis	IgA & C3	rare
Chronic Bullous Disease of Childhood or Linear IgA SBD	unknown	BMZ	IgA	rare

* DIF - direct immunofluorescence

** IIF - indirect immunofluorescence

REFERENCES

Ackerman AB, Penneys NS and Clark WH: Erythema multiforme exudativum: Distinctive pathologic process. Brit J Dermatol 84:554, 1971

Ackerman AB: Histologic Diagnosis of Inflammatory Skin Disease. Lea & Febiger, Philadelphia, 1978

Ahmed AR, Graham J, Jordon RE and Provost TT: Pemphigus: Current concepts. Ann Int Med 92:396, 1980

Anwar ARE and Kay AB: The ECF-A tetrapeptides and histamine selectively enhance human eosinophil complement receptors. Nature 269:522, 1977

Anwar ARE and Kay AB: Enhancement of human eosinophil complement receptors by pharmacologica mediators. J Immunol 121:1245, 1978

Baba T, Sonozaki H, Seki K, et al.: An eosinophil chemotactic factor present in blister fluids of bullous pemphigoid patients. J Immunol 116:112, 1976

Barranco VP: Mixed bullous disease. Arch Dermatol 110:221, 1975

Barvey A, Lazarus GS and Barland P: Basement membrane antibody with skin bullae. N Y State J Med 76:2127, 1976

Batchelor JR, Welsh RI, Tinoco RM, et al.: Hydralazine-induced lupus erythematosus: Influence of HLA-DR and sex in susceptibility. Lancet i:1107, 1980

Bean SF and Lynch FW: Senear-Usher syndrome: Pemphigus erythematosus, immunofluorescent studies in a patient. Arch Dermatol 101:642, 1970

Bean SF: Cicatricial pemphigoid: Immunofluorescence studies. Arch Dermatol 110:552, 1974

Bean SF, Michel B, Furey N, Thorne EG and Meltzer L: Vesicular pemphigoid. Arch Dermatol 112:1402, 1976

Beutner EH, Jordon R: Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescence staining. Proc Soc Exp Biol Med 117:505, 1964

Beutner EH, Chorzelski TP, Hale WZ, et al.: Autoimmunity in concurrent myasthenia gravis and pemphigus erythematosus. JAMA 203:845, 1968A

Beutner EH, Jordan RE, Chorzelski TP: The immunopathology of pemphigus and bullous pemphigoid. J Invest Dermatol 51:63, 1968B

Beutner EH, Chorzelski TP, Jordon R: Autosensitization in pemphigus and bullous pemphigoid. Springfield. Charles C. Thomas Publisher, pp 85-86, 1970

Brunsting LA, Perry HO: Benign pemphigoid?: A report of seven cases with chronic scarring, herpetiform plaques about the head and neck. Arch Dermatol 74:489, 1957

Bushkell LL, Jordon RE and Goltz RW: Herpes gestationis: New immunologic findings. Arch Dermatol 110:65, 1974

Bystryn JC, Rodriguez J: Absence of intercellular antigens in the deep layers of the epidermis in pemphigus foliaceus. J Clin Invest 61:339, 1978

Callen JP, Anderson TF, Chanda JJ, Taylor WB: The association of bullous pemphigoid with other autoimmune disorder. Arch Dermatol 114:245, 1978

Callen JP, Chanda JJ, Weston W: Dermatitis herpetiformis and thyrotoxicosis. Int J Dermatol 18:219, 1979

Callen JP: Internal disorders associated with bullous disease of the skin. J Am Acad Dermatol 3:107, 1980

Chang CM, et al. as quoted by Saikia NK: Pemphigus and malignancy. Brit J Dermatol 88:407, 1973

Chorzelski TP, Jablonska S and Blaszczyk M: Immunopathologic investigations in the Senear-Usher syndrome. Coexistence of pemphigus and lupus erythematosus. Brit J Dermatol 80:211, 1968

Chorzelski TP, Maciejowski E, Jablonska S, et al: Coexistence of pemphigus and bullous pemphigoid. Arch Dermatol 109:849, 1974

Chorzelski TP: Juvenile dermatitis herpetiformis versus "benign chronic bullous dermatosis of childhood". Are these immunologic diseases? J Invest Dermatol 65:447, 1975

Chorzelski TP, Jablonska S, Beutner EH, et al.: Herpes gestationis with identical lesions in the newborn. Arch Dermatol 112:1129, 1976

Chorzelski TP and Jablonska S: IgA linear dermatosis of childhood (chronic bullous diseases of childhood). Brit J Dermatol 101:535, 1979

Comaish JS and Kerr DN: Erythema multiforme and nephritis. Brit J Dermatol 2:84, 1961

Combs RC and Hazelrigg DE: Dermatitis herpetiformis and membranous glomerulonephritis. Cutis 25:660, 1980

Cormane RH: Immunofluorescence studies of the skin in lupus erythematosus and other diseases. Pathol Eur 2:170, 1967

Cream JJ, Scott GL: Anemia in dermatitis herpetiformis. Brit J Dermatol 82:333, 1970

Davies MG, Marks R and Waddington E: Simultaneous systemic lupus erythematosus and dermatitis herpetiformis. Arch Dermatol 112:1292, 1976

Davies MG, Marks R, Nuki G: Dermatitis herpetiformis - a skin manifestation of a generalized disturbance in immunity. Q J Med 47:221, 1978

DeMento FJ and Grover RW: Acantholytic herpetiform dermatitis. Arch Dermatol 107:883, 1973

Deng J, Beutner EH, Shu S, Chorzelski TP: Pemphigus antibody action on skin explants. Arch Dermatol 113:923, 1977

Diaz LA, Glamb RW, Silva J Jr.: A syndrome of multiple immune autoreactivity. Arch Dermatol 116:77, 1980

Diaz-Perez JL and Jordon RE: The complement system in bullous pemphigoid. IV. Chemotactic activity in blister fluids. Clin Immunol & Immunopathol 5:360, 1976

Emmerson RW, Wilson-Jones E: Eosinophilic spongiosis in pemphigus. Arch Dermatol 97:252, 1968

Eng AM and Moncada B: Bullous pemphigoid and dermatitis herpetiformis: Histopathologic differentiation of bullous pemphigoid and dermatitis herpetiformis. Arch Dermatol 110:51, 1974

Falk ES: Pemphigus foliaceus in a patient with rheumatoid arthritis and Sjogren's syndrome. A case report. Dermatologica 158:348, 1979

Farb RM, Dykes R, Lazarus GS: Anti-epidermal-cell-surface pemphigus antibody detaches viable epidermal cells from culture plates by activation of proteinase. Proc Natl Acad Sci USA 75:459, 1978

Forman L: Pemphigus vegetans of Hallopeau. Arch Dermatol 114:627, 1978 (letter)

Fraser NG, Rennie AGR, Donald D: Dermatitis herpetiformis and Sjogren's syndrome. Brit J Dermatol 100:213, 1979

Freeman RG: Personal communication, 1980

Freiburger D: Pemphigus erythematosus. Arch Dermatol 104:449, 1971

From E and Fredericksen P: Pemphigus vulgaris following D-penicillamine. Dermatologica 152:358, 1976

Fry L, Keir P, McMinn RMH, Cowan JD and Hoffrand AV: Small intestine structure and function and hematologic changes in dermatitis herpetiformis. Lancet 2:729, 1967

Fry L, Seah PP, Riches DJ and Hoffbrand AV: Clearance of skin lesions in dermatitis herpetiformis after gluten withdrawal. Lancet 1:288, 1973

Fudenberg HH, Spitler LE and Levin AS: Amer J Pathol 69:529, 1972

Gebhard RL, Falchuk ZM, Katz SI, Sessoms C, Rogentine GN and Strober W: Dermatitis herpetiformis: Immunologic concomitants of small intestinal disease and relationship to histocompatibility antigen HL-A8. J Clin Invest 54:98, 1974

Giannini JM, Callen JP, Gruber GG: Bullous pemphigoid and rheumatoid arthritis. (Submitted for publication)

Gianotto F: The action of ACTH on blood histomine and eosinophil leukocytes in a case of herpes gestationis. J Allergy 25:472, 1954

Gilliam JN and Prystowsky SD: Mixed connective tissue disease syndrome. Cutaneous manifestations of patients with epidermal nuclear staining and high titer serum antibody to ribonuclease-sensitive extractable nuclear antigen. Arch Dermatol 113:583, 1977

Goodnough LT, Muir A: Bullous pemphigoid as a manifestation of chronic lymphocytic leukemia. (Submitted for publication)

Greaves MW, Burton JL, Marks J and Dawber RPR: Azathioprine in treatment of bullous pemphigoid. Brit Med J 1:144, 1971

Hamilton DB, MacKenzie AW: Bullous pemphigoid in primary biliary cirrhosis. Brit J Dermatol 99:447, 1978

Hardy KM, Perry HO, Pingree GC, et al.: Benign mucous membrane pemphigoid. Arch Dermatol 104:467, 1971

Harrington CI and Reed NW: Dermatitis herpetiformis: Effect of gluten-free diet on skin IgA and jejunal structure and function. Brit Med J 1:872, 1977

Harrington CI, Sneadon IB, Walker AE: Pemphigus vulgaris in a 15-year old girl. Acta Derm Venereol (Stockh). 58:277, 1978

Harrington CI, Sneddon IB: Coexistence of bullous pemphigoid and pemphigus foliaceus. Brit J Dermatol 100:441, 1979

Hausmanowa-Petrusewicz I, Chorzelski T, Strugalska H: Three-year observation of a myasthenic syndrome concurrent with other autoimmune syndromes in a patient with thymoma. J Neurol Sci 9:273, 1969

Heading RC, Paterson WD, McClelland DBL, Barnetson RSC and Murry MSM: Clinical response of dermatitis herpetiformis skin lesions to a gluten-free diet. Brit J Dermatol 94:509, 1976

Heine KG, Kumar A, Jordon RE: Pemphigus-like antibodies in bullous pemphigoid. Arch Dermatol 113:1693, 1977

Hermann K, Lohrisch I, Bohme HJ, et al.: Detection of antibodies after immune complex splitting in serum of patients with bullous pemphigoid and systemic lupus erythematosus. Brit J Dermatol 99:635, 1978

Hertz KC, Katz SI, Maise J and Ackerman B: Herpes gestationis. A clinical pathologic study. Arch Dermatol 112:1543, 1976

Holubar K, Doralt M and Eggerth G: Immunofluorescence patterns in dermatitis herpetiformis. Brit J Dermatol 85:505, 1971

Holubar K, Beutner EH: Pemphigus vs acantholytic herpetiform dermatitis. Arch Dermatol 109:408, 1974

Holubar K, Wolff K, Konrad K and Beutner EH: Ultrastructural localization of immunoglobulins in bullous pemphigoid skin. J Invest Dermatol 64:220, 1975

Honeyman JF, Honeyman A, Lobitz WC and Storrs FJ: The enigma of bullous pemphigoid and dermatitis herpetiformis. Arch Dermatol 106:22, 1972

Honeyman JF, Honeyman AR, De la Parra MA, Pinto A, Eguiguren GJ: Polymorphic pemphigoid. Arch Dermatol 115:423, 1979

Imamura S, Takigawa M, Ikai K, et al.: Pemphigus foliaceus, myasthenia gravis, thymoma and red cell asplasia. Clin Exp Dermatol 3:285, 1978

Inderbitzin TM and Grob PJ: Destruction of epithelial cells in vivo by antiepithelial autoantibodies. J Invest Dermatol 49:642, 1967

Jablonska S, Chorzelski T and Blaszczyk M: Immunosuppressants in the treatment of pemphigus. Brit J Dermatol 83:315, 1970A

Jablonska S, Chorzelski T, Leboida J: Co ris tenz von pemphigus erythematosus and myasthenia gravis. Hautarzt 21:156, 1970B

Jablonska S: Juvenile dermatitis herpetiformis in the light of immuno-fluorescence studies. Brit J Dermatol 85:307, 1971

Jablonska S, Chorzelski TP, Beutner EH and Chorzelski J: Herpetiform pemphigus, a variable pattern of pemphigus. Interna J Dermatol 14:353, 1975

Jablonska S, Chorzelski T, Blaszczyk M, Maciejewski W: Pathogenesis of pemphigus erythematosus. Arch Dermatol Res 258:135, 1977

Jacobs R, Eng AM, Solomon LM: Carcinoma of the breast, pemphigus vulgaris and gyrate erythema. Int J Dermatol 17:221, 1978

Jauregui HO: Lymphomatoid granulomatosis after immunosuppression for pemphigus. Arch Dermatol 114:1052, 1978

Jones RR and Goolamali SK: IgA bullous pemphigoid: A distinct blistering disorder. Brit J Dermatol 102:719, 1980

Jordon RE, Beutner EH, Wtesbsky E, et al.: Basement zone antibodies in bullous pemphigoid. JAMA 200:751, 1967

Jordon RE, Muller SA, Hale WL, Beutner EH: Bullous pemphigoid associated with systemic lupus erythematosus. Arch Dermatol 99:17, 1969A

Jordon RE, Sams WM, Beutner EH: Complement immunofluorescence staining in bullous pemphigoid. J Lab Clin Med 74:548, 1969B

Jordon RE, Sams WM Jr., Diaz G and Beutner EH: Negative complement immunofluorescence in pemphigus. J Invest Dermatol 57:407, 1971

Jordon RE, Bean SF, Jablonska S, et al.: Chronic nonhereditary childhood bullous diseases. Beutner EH, Chorzelski TB, Bean SF, et al. (eds) Immunopathology of the Skin: Labeled Antibody Studies. Stroudsburg, Hutchison and Ross, Inc. page 78, 1973A

Jordon RE, Day NK, Sams WM: The complement system in bullous pemphigoid. I. Complement and complement levels in serum fluids. J Clin Invest 52:1207, 1973B

Jordon RE, Day NK, Luckasen JR, Good RA: Complement activation in pemphigus vulgaris blister fluid. Clin Exp Immunol 15:53, 1973C

Jordon RE: Complement activation in bullous diseases. J Invest Dermatol 65:162, 1975

Jordon RE, Nordby-McFarland JM and Tappenier G: The complement system in bullous pemphigoid. V. In vitro fixation of properdin by pemphigoid antibody. J Clin Lab Immunol 1:59, 1978

Kahn G, Lewis HM: True childhood pemphigus: Pemphigus foliaceus in an 18-month old child: Immunofluorescence as a diagnostic aid. Am J Dis Child 121:253, 1971

Kalimo K: Rheumatoid factor in sera of dermatitis herpetiformis patients. Brit J Dermatol 98:79, 1978

Kapeller-Adler R: The effects of steroid hormones and of gonadotropins on histaminase. Biochem J 48:21, 1951

Katz A, Minta JO, Twole JWP, et al.: Immunopathologic study of herpes gestationis in mother and infant. Arch Dermatol 113:1069, 1977

Katz AL, Nashel DJ, Goard CP, et al.: Pemphigus vulgaris and lymphoma in a patient with scleroderma. South Med J 72:1463, 1979

Katz SI, Falchuk ZM, Dahl MV, Rogentine GN and Strober W: HL-A8: A genetic link between dermatitis herpetiformis and gluten-sensitive enteropathy. J Clin Invest 41:2977, 1972

Katz SI, Dahl MV, Penneys N, Trapani RJ and Rogentine N: HL-A antigens in pemphigus. Arch Dermatol 108:53, 1973

Katz SI, Falchuk ZM, Dahl MV, Rogentine GN and Strober W: HL-A8: A genetic link between dermatitis herpetiformis and gluten-sensitive enteropathy. J Clin Invest 41:2977, 1972

Katz SI, Hertz KC and Yaoita H: Herpes gestationis: Immunopathology and characterization of the HG factor. J Clin Invest 57:1434, 1976

Katz SI, et al.: Effect of sulfones on complement deposition in dermatitis herpetiformis and on complement mediated guinea pig reactions. J Invest Dermatol 67:688, 1977

Kavli G: Pemphigus vulgaris and thymoma. A T-lymphocyte defect? Brit J Dermatol 99:97, 1978

Kay AB, Duncan AJ, Glass EJ and Stewart J: Leukocyte chemotactic factors and the C3b receptors. In Proceedings of the 4th International Symposium on the Biochemistry of the Acute Allergic Reactions, May 1980, in press

Kennedy C, Hodge L, Sanderson KV: Skin changes caused by d-penicillamine treatment of arthritis. Clin Exp Dermatol 3:107, 1978

Knight AG, et al.: Eosinophilic spongiosis; a clinical histological and immunofluorescent correlation. Clin Exp Dermatol 1:141, 1976

Kough RH, Barnes WT: Thymoma associated with erythroid apalasia, bullous skin eruption and the lupus erythematosus cell phenomenon: Report of a case. Ann Intern Med 61:308, 1964

Krain LS, Landau JW and Newcomer VD: Cyclophosphamide in the treatment of pemphigus vulgaris and bullous pemphigoid. Arch Dermatol 106:657, 1972

Krain LS, Terasaki PI, Newcomer VD, et al.: Increased frequency of HL-A-10 in pemphigus vulgaris. Arch Dermatol 108:803, 1973

Krain LS: The association of pemphigus with thymoma or malignancy. A critical review. Brit J Dermatol 90:397, 1974A

Krain LS: Pemphigus: Epidemiologic and survival characteristics of 59 patients, 1955-1973. Arch Dermatol 110:862, 1974B

Krain LS, Bierman SM: Pemphigus vulgaris and internal malignancy. Cancer 33:1091, 1974C

Kristensen JK, Wadskov S: Penicillamine induced pemphigus foliaceus. Arch Derm Venereol (Stockh) 57:69, 1977

Kumar PJ and Dawson AM: Dermatitis herpetiformis associated with pernicious anemia and thyrotoxicosis. Proc R Soc Med 66:1128, 1973

Lancaster-Smith M, Kumar P, Clark ML, Marks R and Johnson GD: Antireticulin antibodies in dermatitis herpetiformis and adult celiac disease: Their relationship to a gluten-free diet and jejunal histology. Brit J Dermatol 92:37, 1975

Lawley TJ, Strober W, Yaoita H and Katz SI: Small intestinal biopsies and HLA types in dermatitis herpetiformis. Patients with granular and linear IgA skin deposits. J Invest Dermatol 74:9, 1980

Lever WF: Pemphigus. Medicine (Baltimore) 32:1, 1953

Lever WF and White H: Treatment of pemphigus with corticosteroids. Arch Dermatol 87:12, 1963

Lever WF: Methotrexate and prednisone in pemphigus vulgaris. Arch Dermatol 106:491, 1972

Lever WF and Schaumburg-Lever G: Histopathology of the Skin. J. B. Lippincott Company. Page 116, 1975

Lever WF, Schaumburg-Lever G: Immunosuppressants and prednisone in pemphigus vulgaris: Therapeutic results obtained in 63 patients between 1961 and 1975. Arch Dermatol 113:1236, 1977

Lever WF: Pemphigus and pemphigoid. A review of advances made since 1964. J Am Acad Dermatol 1:2, 1979

Lillicrap DA: Rheumatoid arthritis and pemphigoid. Proc R Soc Med 56:921, 1963

Mackie RM, Saikia NK, Morley WN: Case of pemphigus vulgaris in association with Addisonian pernicious anemia. Brit J Dermatol 88:139, 1973

Mann DL, Katz SI, Nelson DL, Abelson LD, Strober W: Specific B cell antigens associated with gluten-sensitive enteropathy and dermatitis herpetiformis. Lancet 1:110, 1976

Marks J, Shuster S and Watson AJ: Small bowel changes in dermatitis herpetiformis. Lancet 2:1280, 1966

Marks J and Shuster S: Dermatitis herpetiformis: The role of gluten. Arch Dermatol 101:452, 1970

Marsden RA, Ryan TJ, Vanhegan RI, et al.: Pemphigus foliaceus induced by penicillamine. Brit Med J 2:1423, 1976

Marsden RA, Dawber RPR, Millard PR, et al.: Herpetiform pemphigus induced by penicillamine. Brit J Dermatol 97:451, 1977

McKee PH, McClelland M, Sandford JC: Co-existence of pemphigus, anti-skeletal muscle antibody and a retorperitoneal paraganglioma. Brit J Dermatol 99:441, 1978

Michel B, Ko CS: Effect of pemphigus or bullous pemphigoid sera and leukocytes on normal skin in organ culture. An in vitro model for the study of bullous diseases. J Invest Dermatol 62:541, 1974 (abst.)

Michel B, Ko CS: An organ culture model for the study of pemphigus acantholysis. Brit J Dermatol 96:295, 1977

Miller JF, et al.: Coexistence of bullous pemphigoid and systmic lupus erythematosus. Cutis 21:368, 1968

Millikan LE and Conway FR: Effects of drugs on the pilamar pathway. Paper read at the 25th annual meeting of the SID, Chicago, Illinois, July 21-23, 1974

Monacada B: Dermatitis herpetiformis: In association with systemic lupus erythematosus. Arch Dermatol 109:723, 1974

Mondino BJ, Brown SI and Rabin BS: HLA antigens in ocular cicitricial pemphigoid. Brit J Ophthalmo 62:265, 1978

Mowbray JF, Hoffbrand AV, Holborow EJ, Seah PP and Fry L: Circulating immune complexes in dermatitis herpetiformis. Lancet 1:400, 1973

Muller SA, Hermann Ed Jr., Windelmann RK: Herpes simplex infection in hematologic malignancies. Am J Med 52:102, 1972

Noguchi S, Nishitani H: Immunologic studies of a case of myasthenia gravis associated with pemphigus vulgaris after thymectomy. Neurology 26:1075, 1976

O'Loughlin S, Goldman GC, Provost TT: Fate of pemphigus antibody following successful therapy: Preliminary evaluation of pemphigus antibody determinations to regulate therapy. Arch Dermatol 114:1769, 1978

Osteen FB, Wheeler CE, Briggaman RA, Puritz EM: Pemphigus foliaceus. Early clinical appearance as dermatitis herpetiformis with eosinophilic spongiosis. Arch Dermatol 112:1148, 1976

Park MS, Ahmed AR, Terasaki PI, et al.: HLA-DRW4 in 91% of Jewish pemphigus vulgaris patient. Lancet ii:441, 1979

Peck SM, Lefkovits AM: Bullous pemphigoid and polymyositis in coexisting contact dermatitis. Arch Dermatol 94:672, 1966

Peck SM, Osserman KE, Weiner LB, et al.: Studies in bullous diseases. N Engl J Med 279:951, 1968

Peck GL, Herzig GP and Elias PM: Toxic epidermal necrolysis in a patient with graft-vs-host reaction. Arch Dermatol 105:561, 1972

Pedro SD and Dahl MV: Direct immunofluorescence of bullous systemic lupus erythematosus. Arch Dermatol 107:118, 1973

Pehamberger H, Gschnait F, Konrad K and Kolubar K: Bullous pemphigoid, herpes gestationis and linear dermatitis. Herpetiformis: Circulating anti-basement membrane zone antibodies, in vitro studies. J Invest Dermatol 74:105, 1980

Penneys NS, Eaglstein WH, Indign S and Frost P: Gold sodium thiomalate treatment of pemphigus. Arch Dermatol 108:56, 1973

Penneys NS, Ziboh V, Gottlieb NL and Katz SI: Inhibition of prostaglandin synthesis and human epidermal enzymes by autothiomalate in vitro: possible actions of gold in pemphigus. J Invest Dermatol 63:356, 1974

Penneys NS, Eaglstein WH, Frost P: Management of pemphigus with gold compounds: a long-term follow-up report. Arch Deramtol 112:185, 1976

Perry HO, Brunsting LA: Pemphigus foliaceus. Further observations. Arch Dermatol 91:10, 1965

Person JR, Rogers RS: Bullous and cicatricial pemphigoid. Mayo Clin Proc 52:54, 1977

Piamphongsant T and Ausawamongkonpan S: Bullous pemphigoid controlled by dapsone. Dermatologica 152:352, 1976

Pisanty S, Garfunkel A: Kaposi's sarcoma. J Oral Med 25:89, 1970

Provost TT and Tomasi TB: Evidence for complement activation via the alternate pathway in skin diseases. I. Herpes gestationis, systemic lupus erythematosus and bullous pemphigoid. J Clin Invest 52:1779, 1973

Provost TT and Tomasi TB: Evidence for activation of complement via alternate pathway in skin diseases. II. Dermatitis herpetiformis. Clin Immunol 3:175, 1974

Prystowsky SD and Gilliam JN: Benign chronic bullous dermatosis of childhood. Arch Dermatol 112:837, 1976

Reunala T, Blomquist K, Tarpila S, et al.: Gluten free diet in dermatitis herpetiformis. Brit J Dermatol 97:473, 1977

Riches DJ, Martin BGH, Seah PP and Fry L: Ultrastructural observations on uninvolved skin in dermatitis herpetiformis. Brit J Dermatol 88:323, 1973

Riches DJ, Martin BGH, Seah PP and Fry L: The ultrastructural changes in the skin in dermatitis herpetiformis after withdrawal of dapsone. Brit J Dermatol 94:31, 1976

Roenigk HH and Deodhar S: Pemphigus treatment with azathioprine. Arch Dermatol 107:353, 1973

Rogers RS, et al.: Immunopathology of cicitricial pemphigoid. Studies of complement deposition. J Invest Dermatol 68:39, 1977

Rosenberg FR, Sanders S and Nelson CT: Pemphigus: A 20-year review of 107 patients treated with corticosteroids. Arch Dermatol 112:962, 1976

Rosenmann E: Kaposi's sarcoma in a patient with pemphigus vulgaris. Isr J Med Sci 2:269, 1966

Ruocco V, Rosse A, Argenziano G, Astarita C, Alviggi L, Farzati B, Papaleo G: Pathogenecity of the intercellular antibodies of pemphigus and their periodic removal from the circulation by plasmapheresis. Brit J Dermatol 98:237, 1978

Ruocco V, Rossi A, Pisani M, et al.: An abortive form of pemphigus vulgaris probably induced by penicillin. Dermatologica 159:159:266, 1979

Ryan JG: Pemphigus: A 20-year survey of experience with 70 cases. Arch Dermatol 104:14, 1971

Safai B, Gupta S, Good RA: Pemphigus vulgaris associated with a syndrome of immunodeficiency and thymoma: A case report. Clin Exp Dermatol 3:129, 1978

Saikia NK: Extraction of pemphigus antibodies from a lymphoid neoplasm and its possible relationship to pemphigus vulgaris. Brit J Dermatol 86:411, 1972A

Saikia NK, MacConnell LES: Senear-Usher syndrome and internal malignancy. Brit J Dermatol 87:1, 1972B

Salo OP and Rasanen JA: Pemphigoid and rheumatoid arthritis, clinical and immunological study. Ann Clin Res 4:173, 1972

Sams WM Jr. and Jordon RE: Correlation of pemphigoid and pemphigus antibody titers with activity of disease. Brit J Dermatol 84:7, 1971A

Sams WM, Jordon RE: Pemphigus antibodies: Their role in disease. J Invest Dermatol 56:474, 1971B

Savin JA: International mortality from bullous disease since 1950. Brit J Dermatol 94:179, 1976

Savin JA: The events leading to the death of patients with pemphigus and pemphigoid. Brit J Dermatol 101:521, 1979

Schroeter A, Sams WM Jr., Jordon RE: Immunofluorescent studies of pemphigus foliaceus in a child. Arch Dermatol 100:736, 1969

Schiltz J, Michel B: Production of epidermal acantholysis in normal human skin in vitro by the IgG fraction from pemphigus serum. J Invest Dermatol 67:254, 1976

Schiltz J, Michel B, Papay R: Pemphigus antibody interaction with human epidermal cells in culture. A proposed mechanism for pemphigus acantholysis. J Clin Invest 62:778, 1978

Schiltz JR, Michel B, Papay R: Appearance of "pemphigus acantholysis factor" in human skin cultured with pemphigus antibody. J Invest Dermatol 73:575, 1979

Seah PP, Fry L, Hoffbrand AV and Holborow EJ: Tissue antibodies in dermatitis herpetiformis and adult celiac disease. Lancet 1:834, 1971

Seah PP, Fry L, Stewart JS, Chapman BL, Hoffbrand AV and Holborow EJ: Immunoglobulins in the skin in dermatitis herpetiformis and celiac disease. Lancet 1:611, 1972

Seah PP, Fry L, Cairns RJ, et al.: Pemphigus controlled by sulfapyradine. Brit J Dermatol 89:77, 1973A

Seah PP, Fry L, Mazaberi MR, Mowbray JF, Hoffbrand AV and Holborow EJ: Alternate pathway complement fixation by IgA in skin in dermatitis herpetiformis. Lancet 2:175, 1973B

Seah PP and Fry L: Immunoglobulins in skin in dermatitis herpetiformis and their relevance in diagnosis. Brit J Dermatol 92:157, 1975

Shu S-Y, Beutner EH: Isolation and chacterization of antigens reactive with pemphigus antibodies. J Invest Dermatol 61:270, 1973

Sneddon I, Church R: Pemphigus foliaceus presenting as dermatitis herpetiformis. Arch Derm Venereol (Stockh) 47:440, 1967

Sontheimer RD, Garabaldi R and Krueger GG: Stevens-Johnson Syndrome and its association with mycoplasma pneumonia infections. Arch Dermatol 114:241, 1978

Sparrow PG: Penicillamine, pemphigus and the nephrotic syndrome occurring spontaneously. Brit J Dermatol 98:103, 1978

Spigel GT, Winkelmann RK: Cicatricial pemphigoid and rheumatoid arthritis. Arch Dermatol 114:415, 1978

Stastny P: Association of the B-cell alloantigen DRW4 with rheumatoid arthritis. N Engl J Med 298:869, 1978

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

Stillman MA, Baer RL: Pemphigus and thymoma. Acta Derm Venereol (Stockh). 52:393, 1972

Stingl G, Honigsmann H, Holubar K and Wolff K: Ultrastructural localization of immunoglobulins in skin of patients with dermatitis herpetiformis. J Invest Dermatol 67:507, 1976

Stone SP, Schroeter AL: Bullous pemphigoid and associated malignant neoplasm. Arch Dermatol 111:991, 1975

Sullivan TJ: The role of eosinophils in inflammatory reactions. Progress in Hematology, Volume 11, E. B. Brown, ed. Frune, Stratton, Inc., page 65, 1979

Takigawa M, Imamura S: Experimental production of rabbit anti-guinea-pig epidermal cell sera: comparison to pemphigus antibodies. J Invest Dermatol 68:259, 1977

Takigawa M, Imamura S, Ofuji S: Surface distribution of pemphigus antibody-binding substance(s) on isolated guinea pig epidermal cells: an immunoferritin electron microscopy study. J Invest Dermatol 71:182, 1978

Tan SG and Rowell NR: Pemphigus-like syndrome induced by D-penicillamine. Brit J Dermatol 95:99, 1976

Tedesco AS, Lynch PJ: Association of dermatitis herpetiformis and pernicious anemia. Arch Dermatol 115:1117, 1979

Terpstra H, De Jong MCJM, Klokke AH: In vivo bound pemphigus antibodies in a stillborn infant: Passive intrauterine transfer of pemphigus vulgaris? Arch Dermatol 115:316, 1979

Thomsen K and Schmidt H: PUVA-induced bullous pemphigoid. Brit J Dermatol 95:568, 1976

Uhlin SR, Maiocco KH, Bhatia SG: Pemphigus erythematosus and thymoma. Cutis 25:177, 1980

Van der Meer JB: Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis. An immunofluorescent study. Brit J Dermatol 81:493, 1969

Van der Meer JB: Dermatitis Herpetiformis: A Specific Immunopathological Entity. Published by the author. 1972

Van der Meer as quoted by Lever, Lever WF and Schaumburg-Lever G: Histopathology of the Skin. J. B. Lippincott Company. 1975

Van der Meer JB, et al.: IgA antibasement membrane antibodies in a boy with pemphigoid. Arch Dermatol 113:1462, 1977

Van Joost T, Crone RA and Overdijk AD: Ocular cicatricial pemphigoid associated with practolol therapy. Brit J Dermatol 94:447, 1976

Vandersteen PR, Jordon RE: Dermatitis herpetiformis with discoid lupus erythematosus. Arch Dermatol 110:95, 1974

Vetters JM, Saikia NK, Wood J, et al.: Pemphigus vulgaris and myasthenia gravis. Brit J Dermatol 88:437, 1973

Wallach D, Pecking A, Delvincourt C, et al.: Syndrome de Gougerot-Sjogren et pemphigus. Evoluation parallele du syndrome sec et de la dexmatose auto-immune. Ann Dermatol Venereol 106:181, 1979

Whittingham S and MacKay JR: The "pemphigus" antibody and immunopathies affecting the thymus. Brit J Dermatol 84:1, 1971

Winkelmann RK, Roth HL: Dermatitis herpetiformis with acantholysis and pemphigus with response to sulfonimides. Arch Dermatol 82:385, 1960

Wintroub BU, Mihm MC, Goetzl EJ, Soter NA and Austen KF: Morphologic and functional evidence for release of mast-cell products in bullous pemphigoid. N Engl J Med 298:417, 1978

Wolf RE, Fudenberg HH and Gilliam JN: Transfer factor therapy in a case of pemphigus vegetans with chronic mucocutaneous candidiasis. Clin Immunol & Immunopath 10:292, 1978

Wood GW, Beutner EH, et al.: Studies in immunodermatology. II. Production of pemphigus-like lesions by intradermal injection of monkeys with Brazilian pemphigus foliaceous sera. Intern Arch Allergy Appl Immunol 41:556, 1972

Wood GW, Beutner EH: Blocking-immunofluorescence studies on the specificity of pemphigus autoantibodies. Clin Immunol & Immunopathol 7:168, 1977

Wright P: Untoward effects with practolol administration: Oculomucocutaneous syndrome. Brit Med J 1:595, 1975

Yaoita H and Katz SI: Immunoelectronmicroscopic localization of IgA in skin of patients with dermatitis herpetiformis. J Invest Dermatol 67:502, 1976A

Yaoita H, Gullino MF and Katz SI: Herpes gestationis, ultrastructure and ultrastructural localization of in vivo bound complement: Modified tissue preparation and processing for horseradish peroxidase staining of skin. J Invest Dermatol 66:383, 1976B

Yaoita H, Hertz K and Katz S: Dermatitis herpetiformis: Immuno-electron microscopic and ultrastructural studies of a patient with linear deposition of IgA. J Invest Dermatol 67:691, 1976C

Zone JJ, LaSalle BA and Provost TT: Characterization of IgA immune complexes in patients with dermatitis herpetiformis. Clin Res 28:2:586A, 1980

NONHEREDITARY CHRONIC BLISTERING DISEASES

APPENDIX

CASE I. Adult Linear IgA Bullous Dermatosis
R.R. (UTHSCD Special Dermatology Clinic Patient)

This 43 year old Mexican man was in good health until 4/77 when he developed a widespread, eczematous dermatitis thought to be a work related allergic contact dermatitis. This eruption cleared with topical steroid creams and 60 mg of triamcinolone IM. Several weeks later he returned with an acute vesicular and bullous eruption involving the medial aspect of his thighs and painful erosions on the buccal mucosa. The appearance of tense bullae and the absence of Nikolsky's sign suggested a diagnosis of bullous pemphigoid. A punch biopsy revealed a subepidermal bullous lesion also consistent with that diagnosis. However, a biopsy for direct immunofluorescence was negative. He was begun on Prednisone 60 mg daily on 5/24/77 with improvement in his generalized bullous dermatosis. He continued to do well over the next two months as the Prednisone dose was tapered to 10 mg every other day.

In August, 1977, he returned to Mexico to visit his family leaving all his medications behind. His disease worsened and he was placed on Dapsone, 100 mg tid, plus 20 mg Prednisone every morning by a Mexican physician. He did well on this combination and it was continued after he returned to the United States.

In October, 1977, he was referred to the UTHSCD Special Dermatology Clinic for further evaluation. On examination he was found to have a generalized, symmetrical, patchy erythema which in many areas assumed an annular or figurate pattern. Many of the erythematous, macular and papular areas were studded with grouped clear vesicles ranging in size from 0.2 to 1 cm. There was involvement of the penis, lips, buccal mucosa and scalp. There were grouped vesicular lesions over the knees and elbows. The clinical appearance suggested either dermatitis herpetiformis or a vesicular form of pemphigoid. Prednisone was discontinued and he was maintained on Dapsone, 100 mg bid.

Biopsies for both light and immunofluorescence microscopy were done. Light microscopy showed neutrophils and eosinophils aggregated in papillary abscesses suggesting dermatitis herpetiformis. Direct immunofluorescent staining of fresh frozen tissue revealed linear IgA and C3 along the epidermal BMZ.

Over the next eighteen months he experienced recurrent exacerbations of his disease which responded slowly (if at all) to a variety of agents. These included sulfones alone and in combination with large doses of steroids, methotrexate, Immuran, and finally Cytoxan. He developed major complications from these drugs, including compression fractures of lumbar vertebra, recurrent infections, and severe (reversible) bone marrow suppression.

He was last seen in August, 1979, under adequate control on Cytoxan 150 mg a day and prednisone, 25 mg every other day.

Comment: This patient illustrates many of the features discussed in the section on linear IgA bullous dermatosis of adults. The clinical picture frequently suggest both BP and DH. The presence of large tense bullous lesions on the medial aspects of the thighs following an eczematous dermatitis and the presence of oral lesions throughout the course of the disease all favor a diagnosis of BP. Since the histopathologic features of BP and DH show considerable overlap, light microscopy may not be helpful in distinguishing these two conditions. Although not performed in this case, recent immunoelectronmicroscopic studies have shown that the IgA antibodies in some of these cases are localized to the lamina lucida, i.e. the same site as IgG binding in BP. In addition, Lawley and Katz (1980) have shown that these patients do not have the expected gluten sensitive enteropathy seen in most if not all patients with typical DH. Finally, patients with linear IgA subepidermal bullous dermatosis do not have an increased prevalence of HLA-B8 and DR3 as seen in patients with DH (Table XIII). For these reasons this conditions seems to be separate from dermatitis herpetiformis and more closely related to bullous pemphigoid.

Most published descriptions of patients with this condition have emphasized that the initial response to Dapsone may be good. Eventually, however, the patients are difficult to manage and poorly responsive to sulfones. This patient has been typical in that regard. Although the diagnosis of linear IgA subepidermal bullous disease may be expected on the basis of clinical findings it can only be definitely established by examining fresh tissue for linear IgA deposits by direct immunofluorescent staining.

Reference: Lawley TJ, Strober W, Yaoita H, Katz SI: Small intestinal biopsies and HLA types in dermatitis herpetiformis. Patients with granular and linear IgA skin deposits. J Invest Dermatol 74:9, 1980

TABLE XIII

HLA IN CHRONIC BLISTERING DISEASES

Disease	HLA		
Dermatitis Herpetiformis	-	B8,	DR3
Linear IgA Bullous Dermatosis	-	-	-
Cicatricial Pemphigoid	A3,	B12	-
Pemphigus (non-Jewish)	-	B13	-
Pemphigus (Jewish)	A10,	-	DR4

Katz SI, 1972 and 1973; Krain LS, 1973; Mondino BT, 1978; Park MS, 1979

CASE II. Linear IgA Bullous Dermatosis of Childhood (Chronic Bullous Dermatosis of Childhood)

This previously healthy 2-1/2 year old black boy suddenly developed pruritus and tense bullae on the extremities, lower trunk and genitalia. A rosette pattern was noted in some areas but grouped vesicular lesions were not seen. No mucosal lesions were present. The child seemed otherwise well and a clinical diagnosis of benign chronic bullous dermatosis of childhood was made. He was given sulfapyridine 900 mg daily but after eight weeks this was discontinued. One month later he spontaneously cleared only to suffer several milder periods of blister formation during the next 1-1/2 years. Each attack cleared spontaneously without therapy.

Routine laboratory studies throughout this period were normal. The ESR was slightly elevated at 25 mm/hr. on one occasion. Indirect immunofluorescence studies were negative. Direct immunofluorescence studies of lesional skin showed linear deposits of IgA and C3 along the basement membrane zone of the epidermis. Examination by light microscopy revealed a subepidermal bullous lesions consistent with bullous pemphigoid.

Comment: At the time of this patients initial evaluation in 1974 the observed immunofluorescence findings (i.e. linear IgA along the BMZ) had not been reported. Since that time a number of cases of linear IgA in children with subepidermal blistering diseases have been reported and now there is some agreement that this should be considered a distinct clinical entity. Chorzelski and Jablonska (1979) have recently stated that, "IgA linear dermatosis of childhood (formerly known as chronic bullous disease of childhood) seems to be a distinct entity different from both dermatitis herpetiformis and bullous pemphigoid and is characterized immunopathologically by linear IgA deposits at the basement membrane zone". This condition is characterized clinically by large and often clustered bullae (forming a rosette pattern) chiefly on the lower part of the trunk, pelvic region, groin and thighs and histologically by the presence of subepidermal blisters. According to these and other workers CBDC or linear IgA dermatosis of childhood should be regarded as a counter-part of linear IgA dermatosis of adults. In contrast to DH these cases do not show intestinal involvement or an association with the HLA-B8 and DR3 haplotypes (see Table XIII). According to some, this condition responds to a combination of sulfones and corticosteroids. Sulfones or sulfapyradine alone even in high doses often fail to control this disease.

References: Prystowsky SD and Gilliam JN: Benign chronic bullous dermatoses of childhood. Arch Derm 112:837, 1976; Chorzelski TP and Jablonska S: IgA linear dermatosis of childhood (chronic bullous disease of childhood). Brit J Dermatol 101:535, 1979

CASE III. Herpes Gestationis
B.C., PMH Unit No. 46-40-93

This 30 year old white woman developed an itchy rash in September, 1973, during the fifth month of pregnancy. At the onset the rash involved her hands and arms and was thought to be "poison ivy". Over the next four to six weeks there was gradual extension of the eruption to involve the trunk, neck, face and scalp. The patient had previously had two normal pregnancies. The rash was described as extremely pruritic.

On physical examination she was obviously pregnant and complained bitterly of a widespread cutaneous eruption. Except for the skin the findings were unremarkable. The skin lesions were serpiginious and polycyclic composed of dark red to violaceous plaques covered by vesicles and pustules. The distribution was symmetrical and mainly over the distal upper extremities, neck and face. The clinical impression was herpes gestationis.

Histological examination revealed an intraepidermal, vesicular lesion containing numerous eosinophils. Groups of eosinophils were also present in the papillary dermis. There were no papillary abscesses. Direct fluorescent antibody staining of lesional skin for IgG showed weak staining along the epidermal basement membrane zone. Staining for immunoglobulins A, M, D and E was negative; strong C3, C4 and properdin staining was found along the basement membrane zone.

On 12/2/73 the patient gave birth to a five pound 12 ounce Apgar eight male child. The child had several vesicular and sterile pustular lesions but was otherwise normal. Fluorescent antibody staining of lesional skin showed linear epidermal basement membrane staining for C3, C4 and properdin. A second biopsy from the mother again showed C3, C4 and weak epidermal BMZ IgG staining. A third biopsy obtained from the mother on January 6th, 1974, one month postpartum, revealed IgG, C3, C4 and properdin at the basement membrane zone (see Table XIV). The skin eruption cleared two months after delivery in the mother and a few days after delivery in the child. Several months postdelivery both mother and child were well and without evidence of skin disease.

Comment: This case illustrates the clinical and immunopathologic features of HG. The transient appearance of blisters and C3 bound to the epidermal BMZ in the newborn infant demonstrates passive transfer of this disease from the mother to the child. This is presumed to be due to the transfer of maternal IgG with binding and complement fixing to the epidermal BMZ in the infant. This is apparently only pathogenic when maternal hormones are still present in the baby's circulation. After the pregnancy-related hormonal changes disappeared in the mother and infant the disease was no longer expressed. The clinical and histologic features of this disease show some resemblance to DH, EM and BP. The immunopathologic changes of antibody and complement bound in the lamina lucida area of the BMZ have suggested a close relationship to BP.

TABLE XIV

FINDINGS ON DIRECT FLUORESCENT ANTIBODY STAINING OF SKIN BIOPSIES

	Immunoglobulin					Complement		
MOTHER	IgG	IgA	IgM	IgD	IgE	C3	C4	Proper.
Date of biopsy								
11-5-73	2+	Neg	Neg	Neg	Neg	3+	2+	Neg
12-2-73	1+*	Neg	Neg	Neg	Neg	3+	2+	±
1-6-74	2+*	Neg	Neg	Neg	Neg	4+	2+	2+
BABY								
Date of biopsy								
12-2-73	±*	Neg	Neg	Neg	Neg	4+	2+	2+

* Staining detected after saline extraction of unbound dermal globulin.

CASE IV. Bullous Pemphigoid and Lupus Erythematosus
P.S. (St. Paul Hosp. No. 2558017)

This 29 year old black woman with a history of recurrent arthralgias and Raynaud's phenomenon developed a blistering eruption in February 1980. A skin biopsy revealed a subepidermal blister consistent with the diagnosis of DH. Direct immunofluorescence revealed linear staining for C3 along the dermal epidermal junction and IgG staining of epidermal nuclei. Indirect immunofluorescence was negative. A diagnosis of bullous pemphigoid was made and the patient was begun on systemic steroid treatment with resolution of the blisters. The steroid dose was gradually reduced over the next several weeks.

In July, 1980 she began to notice increasing shortness of breath, PND, orthopnea and peripheral edema. She also had recurrence of blisters and oral erosions. She was hospitalized at Teague General Hospital (Teague, Texas) where a chest x-ray revealed cardiomegaly and bilateral pleural effusions. An LE prep. was positive.

On 8/18/80 she was referred to the UTHSCD for further evaluation and treatment. Physical examination revealed a slightly obese, twenty-nine year old black woman who was oriented and except for mild dyspnea was in no acute distress. Her blood pressure was 160/90, pulse 90 (regular), respirations 28 per minute. She was afebrile. The skin showed scattered, tense bullous lesions over the hands and extremities and several crusted and scarred areas in sites of previous involvement. Several superficial erosions were present on the lips and buccal mucosa. Examination of the chest revealed bilateral basilar rales and dullness. The PMI was palpable in the sixth ICS 2 cm inside the AAL. Her heart rate was regular. The first and second hearts sounds were normal, an S4 was present with a questionable S3. Bilateral pedal edema (2+) was present. There was no cyanosis or clubbing.

Laboratory findings revealed a white blood count of 7,200 per cm^3; hemoglobin 10.2 mg%; hematocrit 31.6 vol.%, BUN 16 mg %; creatinine clearance 1.5 mg %. The urinalysis showed 20 mg % protein, 50 to 60 white blood cells and 20 to 25 red blood cells per high power field.

The patient was treated with Digitalis and diuretics with dramatic improvement in her cardiorespiratory status. She was placed on 40 mg of prednisone (in a divided daily dose) with prompt improvement of her blistering disease. Repeat histology and immunofluorescence of skin biopsies from the skin lesions revealed a subepidermal blister consistent with bullous pemphigoid; IgG and C3 were localized to the epidermal BMZ and IgG was bound to epidermal nuclei. The ANA was pos.(speckled pattern) at a titer > 1:1280, complement levels were slightly depressed and her antiDNA antibody test was positive. Anti-Sm and anti-RNP antibodies were present.

Discharge diagnosis:

(1) systemic lupus erythematosus manifestated by: fever, arthralgias and arthritis, Raynaud's phenomenon, possible myocarditis, antinuclear antibodies (anti-DNA, anti-Sm and anti-nRNP) and a positive LE prep.

(2) Bullous pemphigoid manifested by: tense bullae on both normal and inflammed skin with characteristic histopathologic and immunopathologic findings.

Comment: The initial diagnosis in this patient was dermatitis herpetiformis and the histologic features were consistent with that diagnosis. The clinical picture was not suggestive of DH and the immunopathologic findings of C3 at the BMZ and IgG bound to epidermal nuclei could have suggested LE or MCTD in addition to BP (Gilliam and Prystowsky, 1977). In contrast to this patients condition, DH is intensely pruritic, predominates in males, is rare in blacks, clears with dapsone treatment, responds unpredictably to corticosteroids, and is associated with granular deposits of IgA in the papillary dermis.

Bullous pemphigoid is an acceptable diagnosis in this patient although it is uncommon in young people and oral lesions are usually not present. The immunopathologic findings are consistent with the diagnosis of BP, however, granular IgG and C3 deposits at the basement membrane may be seen in lupus erythematosus. The linear staining pattern suggests BP and circulating anti-BMZ antibody is not found in patients with SLE.

Others have reported cases of SLE in association with DH or BP (Moncada, 1974)(Vandersteen, 1974) (Jordon, 1969)(Kumar, 1978)(Penneys, 1979). Cases of bullae in systemic lupus erythematosus reported in the early 60's by Rothfield and Weismann (1961) may also have been examples of BP, however, precise documentation was impossible since immunopathologic studies were not available at that time.

The recently published cases of BP pemphigoid and coexistent systemic lupus erythematosus have several features in common. Most have been young black women with clinical and serological evidence of active SLE. They have frequently had antinuclear antibodies which produce a speckled staining pattern and several have also been found to have anti-Sm antibodies. Anti-skin basement membrane antibodies have been demonstrated with some difficulty. In a paper by Barvey, Lazarus and Barland (1976), the basement membrane antibodies could only be demonstrated on one of four normal skin substrates. Blocking experiments using pooled BP serum suggested that the antigenic specificity of the antiskin basement membrane antibody was different from BP. The findings suggested that subepidermal eruptions of BP and SLE may be two distinct but similar conditions.

References:

Moncada B: Dermatitis herpetiformis: In association with systemic lupus erythematosus. Arch Dermatol 109:723, 1974

Vandersteen PR, Jordon RE: Dermatitis herpetiformis with discoid lupus erythematosus: Occurrence of sulfone induced discoid lupus erythematosus. Arch Dermatol 110:95, 1974

Jordon RE, Muller SA, Hale WL, et al.: Bullous pemphigoid associated with systemic lupus erythematosus. Arch Dermatol 99:17, 1969

Kumar V, Binder WL, Schotland E, et al.: Coexistence of bullous pemphigoid and systemic lupus erythematosus. Arch Dermatol 114:1178, 1978

Penneys NE, Wiley HE: Herpetiform blisters in systemic lupus erythematosus. Arch Dermatol 115:1427, 1979

Rothfield N and Weissman G: Bullae in systemic lupus erythematosus. Arch Int Med 107:908, 1961

Barvey A, Lazarus GS, Barland P: Basement membrane antibody with skin bullae. New York State J Med 76:2127, 1976

CASE V. Pemphigus Vulgaris
W.S. (St. Paul Hosp no. 2560852)

This 72 year old white woman with ASHD (manifested by angina pectoris) was admitted to St. Paul Hospital in July, 1980, for evaluation of unexplained weight loss and mouth sores. A work-up for occult malignancy and collagen vascular disease was negative. The patient's major complaint was painful sores in her mouth which began in April. These were considered to be due to a yeast infection.

After discharge from the hospital in July, 1980, she began to develop 0.5 to 1 cm flaccid bullous lesions which quickly ruptured to leave expanding painful superficial erosions. These erosions showed no tendency to heal and gradually enlarged by detachment of the epidermis about the margins.

In early August the patient was seen by a dermatologist who made the diagnosis of pemphigus vulgaris. A biopsy showed an intraepidermal blister with acantholytic changes. She was started on 60 mg of prednisone daily and strongly urged to enter the hospital. After treatment as an outpatient for one week without improvement she was admitted for more aggressive treatment.

Examination revealed a well oriented, adequately nourished elderly white woman in moderate distress. She complained of painful mucosal and cutaneous erosions. Examination of the skin and mucous membranes revealed numerous superficial erosions in the mouth, over the upper trunk, back and extremities. The central portion of the cutaneous erosions was covered by a thick adherent crust. The margins were erythematous, moist and showed a collarette of partially detached epidermis. Five to six 0.5 to 1 cm flaccid blisters were seen over the upper back suggesting continued activity of the blistering disease process. The prednisone dose was increased to 100 mg/d.

Laboratory studies revealed normal electrolytes, BUN and creatinine. The WBC was 4200 per mm^3 with a marked left shift. Cultures of the skin lesions, urine and blood were obtained and she was placed in reverse isolation.

On the second hospital day she became acutely short of breath. A chest x-ray revealed cardiomegaly and pulmonary edema. She responded to oxygen, digitalis and diuretics and was transferred to the medical intensive care unit. She was placed on intravenous steroids at a daily dose equivalent to 120 mg of prednisone and her pemphigus appeared to stabilize. Her skin condition seemed to improve slightly over the next several days, however, on the tenth hospital day she became rather lethargic and somewhat confused. That night she was found unresponsive without pulse or respirations and she was pronounced dead.

Comment: Several points deserve emphasis in this elderly woman with typical pemphigus vulgaris. The onset four months prior to her final admission with painful mouth lesions leading to significant weight loss

is a common and frequently unrecognized feature. Had the diagnosis been considered at this stage, serologic histologic or immunopathologic studies could have established the presence of pemphigus and early treatment might have been life saving. According to a recent survey published by Savin (1979). Older pemphigus patients tend to die quickly after the start of steroid therapy, often with extensive skin lesions. The cause of death is usually from conditions such as bronchopneumonia or pulmonary embolism which are not definite steroid side effects. The younger patients, on the other hand, having survived their original illness tend to develop complications such as diabetes and compression fractures which can be attributed to long term high dose corticosteroid treatment.

Lever and Schaumburg-Lever (1977) have outlined two types of treatment depending on the stage of the disease: (1) "high dose prednisone treatment" for pemphigus in the advancing or advanced stage and (2) "combined treatment" of alternate day prednisone plus an immunosuppressant for those patients in the "early stable phase". The "early stable phase" is defined as that period when the disease is localized to one area, which is usually the case for the first several months. The advancing or the advanced stage of the disease is that period following the onset of generalized involvement.

The high dose prednisone regimen, as defined by Lever, is daily doses of prednisone between 180 and 360 mg. If no improvement is evident within five days the daily dose is increased by at least 60 mg. These workers suggest that high doses of prednisone should be administered until all lesions have healed and possibly even beyond that time. This usually requires six to ten weeks of treatment. After completion of high dose treatment the prednisone is quickly reduced to 40 mg daily for one week, 30 mg daily for one week, 25 mg daily for one week and then 40 mg on alternate days. At this point an immunosuppressant (such as Methotrexate 20 mg once a week, cyclophosphamide 100 mg daily or azothioprine 150 mg daily) are added and the prednisone dose gradually reduced and discontinued over several months.

Four patients in the "early stable stage" of pemphigus vulgaris, these workers suggest using combined treatment from the onset. This combined treatment program includes prednisone 40 mg on alternate days and one of the immunosuppressive drugs in the daily dose mentioned above.

Other forms of treatment have been tried with success by several groups. These include immunosuppressants alone, immunosuppressants with high dose prednisone and parenteral gold compounds.

Immunosuppressants alone have been reported as successful treatment of early stable pemphigus vulgaris by several authors (Roenigk and Deodhars, 1973)(Van Diijk and van Velde, 1973). Wolf, et al. initiate treatment with Azothioprine, 100 - 200 mg daily in conjunction with high dose daily prednisone (150 to 200 mg). Cyclophosphamide and prednisone has been used successfully from the onset of disease by Fellner (1978). The principal advantage of using combinations of drugs from the onset

appears to be the ability to reduce the prednisone dose to much lower levels more quickly thus avoiding many of the undesirable steroid side effects.

The most recent addition to the therapeutic armamentarium in pemphigus vulgaris has come from Penneys and coworkers (1973)(1976) who have shown that gold compounds may be useful in the management of these patients. These authors regarded gold as the treatment of choice for pemphigus, after initial control with corticosteroids.

References:

Savin JA: The events leading to the death of patients with pemphigus and pemphigoid. Brit J Dermatol 101:521, 1979

Lever WF and Schaumburg-Lever G: Immunosuppressants and prednisone in pemphigus vulgaris. Therapeutic results obtained in 63 patients between 1961 and 1975. Arch Derm 113:1236, 1977

Roenigk HH, Deodhars S: Pemphigus treated with azothioprine. Arch Dermatol 107:353, 1973

Van Diijk TJA and van Velde JL: Treatment of pemphigus and pemphigoid with azothioprine. Dermatologica 147:179, 1973

Fellner MJ, Katz JM, McCabe JB: Successful use of cyclophosphamide and prednisone for initial treatment of pemphigus vulgaris. Arch Dermatol 114:889, 1978

Penneys NE, Eaglstein WH, Indgins S, et al.: Gold, sodium thiomalate treatment of pemphigus. Arch Deramtol 108:56, 1973

Penneys NS, Eaglstein WH, Frost P: Management of pemphigus with gold compounds: A long term follow-up report. Arch Deramtol 112:185, 1976

CASE VI. Pemphigus Vegetans
L.D. (PMH Unit No. 48-56-45)

This was the first Parkland Hospital admission for this seventeen year old white man with a three month history of painful, spreading lesions of his mouth. He had taken no drugs or medication and had been previously well. The lesions were initially confined to his lips and buccal mucosa causing considerable discomfort and making it difficult for him to eat. The lesions gradually spread to involve the dorsal aspect of his fingers adjacent to fingernails (periungual) and groin region. The patient had been seen by several local physicians who diagnosed a fungal infection (because of the periungual lesions) and prescribed antibiotics without relief. He lost twenty pounds because of his inability to eat.

Physical examination on admission revealed weeping erythematous elevated and vegetating lesions of his lips, nasal alae, chin, chest and abdomen. The lesions appeared pustular and in many areas showed denudation of the surface layers. Erythematous, moist, verrucous lesions about the nail folds, papulovesicular and bullous lesions on the trunk and arms, and red, moist, vegetative lesions of the groin, scrotum and perianal area.were noted. There was no lymphadenopathy and his physical examination was otherwise normal. An initial diagnosis of mucocutaneous candidiasis and bullous impetigo was made.

Laboratory evaluation revealed a white count of 11,800 with 57 polymorphonuclear leukocytes, 16 lymphocytes, 4 monocytes, 10 eosinophils (absolute eosinophil count was 1,008). Platelet count was 322,000. The hemoglobin was 16.3 with a hematocrit was 48.7. Liver function tests, SMA-12, and urinalysis were all within the normal limits. Plasma cortisol was normal. Chest x-ray, barium enema, upper GI series and IVP were all normal. Immunoelectrophoresis revealed a slight increase in IgG and IgA. Antinuclear antibodies and RA latex test were negative. Skin tests for mumps, Tb, histo, cocci and candida were all negative.

Treatment with Amphotericin B was initiated and between September 15th and October 5th he received a total of 375 mg. During this period additional cutaneous blisters developed over the trunk and the intertriginous verrucous lesions were unchanged. Skin biopsies of a cutaneous bulla and of the groin lesion showed typical acantholytic changes with suprabasalar separation typical of pemphigus vulgaris. Direct immunofluorescence showed immunoglobulin bound to the intercellular substance (ICS). Circulating ICS antibody was not detected. A diagnosis of pemphigus vegetans was made and prednisone 80 mg started in a divided daily dose. The bullous lesions of the trunk responded promptly, however, the oral lesions were slow to respond so Methotrexate (50 mg) was added on an every two week basis. Although the lesions improved during the following year, clearing was incomplete and attempts to discontinue methotrexate resulted in worsening of both the mucosal and skin lesions.

In November, 1975, the patient was begun on biweekly injections of dialyzable transfer factor (TF) prepared from leukocytes obtained from random donors (prepared by H. Hugh Fudenberg). At that time he was

continuing to take 40 mg of prednisone every other day. He had not received Methotrexate for two weeks prior to beginning the transfer factor therapy and none was given thereafter. Injections of one transfer factor unit (extract from 5 x 10^8 lymphocytes per ml) were given weekly for the first three weeks, then biweekly for the next six months. After that time he received one TF unit at three to five week intervals. By the 17th week the prednisone was discontinued.

For seventy-seven weeks the patient was maintained on TF alone, and there was marked improvement in all lesions. Treatment with corticosteroids and Methotrexate was not required during this entire time. When transfer factor was subsequently withheld the mucosal and skin lesions flared and the ICS antibody was again present in lesional biopsies. Reinstitution of transfer factor again induced remission with disappearance of ICS antibody.

Comments: This patient demonstrates typical clinical features of pemphigus vegetans of the Neuman variety. This form of pemphigus is often associated with the development of typical bullous lesions in addition to the vegetating lesions often found in the mouth or groin areas. In retrospect it seems likely that the periungual lesions considered to be due to candida were probably lesions of pemphigus vegetans. Such lesions have been well described.

This condition is usually seen in younger patients (as in this case) and has been known to undergo spontaneous remission. The role of the transfer factor in achieving control in this case is unclear. The patient previously responded incompletely to prednisone and Methotrexate. Transfer factor affected an obvious reduction in severity both objectively and subjectively after six weeks. By 18 weeks the lesions completely cleared. Cessation of TF injections was associated with exacerbation which was again reversed when TF therapy was reinstituted. ICS antibody was detected in the groin lesion during the flare but disappeared after resumption of TF therapy.

The following observations suggest that pemphigus may be associated with defective cellular immunity. a) Pemphigus frequently occurs in older individuals in whom T lymphocyte responses are diminished; b) the presence of autoantibodies suggest a pathophysiologic derangement. This is in common with other autoimmune diseases which are thought to be related to abnormalities of cell mediated immunity (possibly through a reduction of suppressor T lymphocytes) (Fudenberg, 1971); c) pemphigus may be associated with disorders such as mysthenia gravis and systemic lupus erythematosus (Beutner, et al. 1968)(Chorzelski, et al., 1968)(Peck, et al., 1968)(Ridley, 1970)(Vetters, et al., 1973). d) Serum antibodies binding to intercellular substance have been found in the sera of some patients with myasthenia gravis, polymyositis and SLE without coexistent pemphigus (Whittingham S and MacKay JR, 1971) (Thivolet J, et al., 1970)(Anderson HJ, et al., 1970).

The effectiveness of transfer factor therapy in this case indicates that this mode of treatment may be beneficial in some patients with milder forms of pemphigus who might otherwise require administration of potent immunosuppressive drugs or corticosteroids in high doses on a long term basis.

References:

Fudenberg HH, Spitler LE and Levin AS: Amer J Pathol 69:529, 1972

Beutner EH, Chorzelski TP, Hale WZ, et al.: JAMA 203:845, 1968

Chorzelski T, Jablonska S and Blaszczyk M: Brit J Dermatol 80:211, 1968

Peck SM, Osserman KE, Weiner LB, et al.: N Engl J Med 279:951, 1968

Ridley CM: Post Grad Med J 46:168, 1970

Vetters JM, Saikia NK, Wood J, et al: Brit J Dermatol 88:437, 1973

Whittingham S and MacKay JR: Brit J Dermatol 84:1, 1971

Thivolet J, et al.: Dermatologica 140:310, 1970

Anderson HJ, et al.: Arch Dermatol 101:538, 1970

CASE VII. Pemphigus Foliaceus
J.C.B. (DVAMC No. 34-27-15)

This 49 year old black man was admitted to the VA Hospital in November of 1973 with a widespread bullous dermatitis. He gave a history of an intermittent blistering skin disease since the age of 33. Since that time he had occasionally received treatment with various topical agents. Upon evaluation he was found to have hypertension, renal insufficiency and anemia. Laboratory studies revealed a creatinine of 2.3 mg/dL, a hematocrit of 29 vol. % and a hemmoglobin of 9.5 grams %. Rheumatoid factor and ANA tests were negative. He was treated with topical steroids and antibiotics for his skin disease and an antihypertensive agent to control his blood pressure. The discharge diagnosis was renal insufficiency (probably secondary to post streptococcal glomerulonephritis) and "infected dermatitis".

He was next seen at the VA hospital in December, 1977, with an exacerbation of his skin condition. A skin biopsy for immunofluorescence revealed ICS antibody in the upper layers of the epidermis. Acantholytic changes were seen in the granular layer by light microscopy consistent with pemphigus foliacous. He was again treated conservatively with topical steroids and systemic antibiotics with moderate improvement. In May, 1978, he was readmitted with E coli sepsis. His skin condition was stable. In September, 1979, he was seen for an exacerbation of his skin lesions. There was obvious secondary infection which was treated with Tegopen. Since that time he has been followed in the Outpatient Department for management of his chronic renal insufficiency and chronic pemphigus foliaceus.

Antinuclear antibody and rheumatoid factor tests have been repeatedly negative. There has been no history of photosensitivity, arthritis, pleurisy, serositis, or other evidence of a collagen vascular disease. His treatment has consisted of topical steroids and emollients, lasix and a variety of antihypertensives. His current diagnoses are: (1) hypertension, (2) chronic renal disease with renal insufficiency, (3) chronic alcoholism, (4) peptic ulcer disease, (5) anemia secondary to chronic renal failure, peptic ulcer disease and alcoholism and (6) pemphigus foliaceus.

Comment: This 56 year old black man probably developed his pemphigus foliaceus at the age of 33. His skin condition was not diagnosed until 21 years after its onset. He has never received systemic steroids or cytotoxic agents for his pemphigus foliaceus which has persisted to a greater or lesser extent throughout this period. This case demonstrates the chronic and relatively benign course that pemphigus foliaceus may pursue.

CASE VIII. Pemphigus Erythematosus
R.K.E. (PMH Unit No. 55-04-41)

R.E., an 18 year old white male was first seen in the Special Dermatology Clinic in 9/76 with a two month history of a blistering eruption which began on the central portion of his chest and spread to involve the malar area of the face, the back, scalp and ears. The initial blisters rapidly broke forming moist, oozing, crusting lesions. He did not have mucosal or genital involvement. Heat and sunlight caused exacerbation of the disease. There was no family history of a similar disease and the general review of systems was negative except for an episode of left external otitis which preceded the onset of the present disease by two weeks.

On physical examination he was found to have diffuse erythema and oozing of the left auditory canal, generalized lymphadenopathy; vesicles and superinfected eroded areas over the central third of his chest, back and malar area. There were also a few scattered lesions on the thighs. There was no evidence of conjunctival or oral involvement.

An LE prep was negative. A biopsy showed acantholysis with a split in the upper dermis consistent with a diagnosis of pemphigus foliceus. He was treated initially with 40 mg of Prednisone a day with very little relief. Because of his failure to respond to Prednisone alone, Methotrexate 50 mg p.o. every other week was added. On this combination his disease promptly responded.

In January, 1979, he developed a non-bullous skin eruption suggestive of lupus erythematosus. Skin biopsy confirmed the diagnosis of cutaneous lupus erythematosus. The antinuclear antibody test was negative but C3 levels were diminished. A diagnosis of subacute cutaneous lupus erythematosus was made. The Methotrexate was stopped and the Prednisone was increased to 20 mg three times a day with a good response. In April of 1979 he was admitted with an exacerbation of his skin rash, arthralgias, myalgias, chills and fever of 103°.

Physical examination revealed a pulse of 100 per minute, blood pressure of 130/50 and a temperature of 102.6°. He was alert and in no acute distress. A widespread skin eruption characterized by numerous erythematous papules and blisters was present over the trunk and extremities. The remainder of his physical examination was within normal limits.

Laboratory evaluation revealed a normal CBC, platelet count, SMA-12, chest x-ray, KUB and EKG. Cultures of the blood, urine, skin lesions, pharnyx, rectum and cerebral spinal fluid were obtained. He was begun on antibiotics and became afebrile within 24 hours. All cultures were negative after 72 hours and the antibiotics were discontinued. The signs and symptoms present on admission did not recur within the next twenty-four hours and on the fourth hospital day he left the hospital against medical advice. The latex fixation test, ANA, and cryoglobulins were negative.

When seen in the clinic on May 2, 1979, he was still taking 60 mg of Prednisone a day and was asymptomatic. The Prednisone was tapered over the next two weeks to 40 mg per day and then 35 mg per day. When last seen in follow-up in August, 1979, he was taking 40 mg of Prednisone on alternate days and remained free of symptoms or abnormal physical findings.

GLOSSARY OF TERMS

Acantholysis - dissolution or separation (-lysis) of intercellular bridges in the prickle-cell layer of the epidermis (acantho-).

Annular - ring-shaped

Arciform - (adj) shaped (-form) in curves (arci-); bent like a bow or bow-shaped

Aphtha - a lesion of the mouth that begins as a painful red macule and evolves into an intensely painful ulcer that heals spontaneously in one to three weeks

Bulla - from Latin meaning anything that becomes round by swelling, like a bubble; a liquid-filled cavity larger than 1 cm in the upper layers of the skin; a blister

Cicatrix - Latin for scar

Circinate - circle shaped

Circumscribed - said of lesions that are sharply limited by clear, distinct borders

Dermatosis - a generic term meaning a pathologic condition (-osis) of the skin (dermat-)

Dermis - refers to the corium alone; what is above or on it is named epidermis

Desmosome - (from Greek) meaning a binding (desmo-) body (-some); a point of attachment of tonofibrils and intercellular bridges on epidermal cells; strongest point of attachment between epidermal cells.

Epidermis - the outermost nonvascular layer of the skin, derived from the embryonic ectoderm, varying in thickness from 0.08 to 0.12 mm and made up of four layers; (1) basal layer or germinal cell layer; (2) spinous layer or prickle-cell layer; (3) granular layer; (4) horny layer or stratum corneum

Eczema - a clinical process that is superficial (principally involving the upper dermis and epidermis) which in its early phases produces erythema, papulovesicular lesions, oozing, weeping and crusting. In later stages the lesions are erythematous, scaly, lichenified and possibly pigmented. The hallmark histologically is the presence of edema in the epidermis (spongiosis).

Epidermolysis - separation (-lysis) of the epidermis; refers to blistering disorders where separation occurs at the dermal-epidermal junction

Epithelium - a cellular lining that is present on the surface of the body structure; the surface may be toward the external world (skin) or toward an internal hollow (as in the case of the gut)

Erythema - redness

Erosion - superficial denudation; loss of a portion or all of the epidermis

Exudation - oozing and weeping of fluid from the surface of the skin, applied to intensely edematous and vesiculating processes

Flaccid - lacking firmness, lax or soft

Foliaceus or foliaceous - from Latin meaning leafy, leaflike; in dermatology a leaflike scale

Furuncle - from Latin furunculus meaning a small-time or petty (-uncle) thief (fur-) used today for boil

Gestationis - pregnancy

Gluten - (Latin meaning glue) the protein of wheat and other grains which gives to the dough its tough elastic character

Gluten sensitive enteropathy (GSE) - nontropical sprue

Herpes - a vesicular process with a tendency for the blisters to form quickly and to cluster; grouped vesicles

Keratin - the protein material that makes up the horny layer or stratum corneum

Lesion - any detectible deviation from normal structure; A primary (or elementary) lesion is defined as the appearance of the first grossly recognizable or most characteristic structural change of skin disease. Secondary lesions are those that evolve or develop as natural progressions from primary lesions or from adventitious events, like scratching, irritation and secondary infection of primary lesions.

-Lysis - a combining form from Greek meaning loosening, separation, dissolution or rupture

Macule - a perceptible change in color on or in the substance of the skin that is not visibly or palpably raised above or depressed below the surrounding level of the skin. Discolorations of skin larger than 1 cm in diameter is usually called a patch.

Multiforme - from Latin meaning of many (multi-) shapes (-forme).

Necrolysis - separation (-lysis) of tissue caused by death (necro-).

Oozing - refers to serous discharge on or from the skin. Associated with crusting from dried serous exudate

Papule - a solid lesion raised above the level of the skin up to 1 cm in diameter. Larger elevated lesions are nodules, tumors or plaques

Papillomatosis - a condition (-osis) marked by tumor formation (-omat-) that consists of many nipple-like (papill-) lesions.

Papillary dermis - the upper mammillated portion of the dermis. The papillary or nipple-like (papill-) projections of the upper dermis which are surrounded by the epidermis.

Pemphigoid - a subepidermal bullous eruption that resembles but is not pemphigus

Pemphigus - Greek pemphix, genitive pemphigos, respectively bubble, of a bubble. Names (with modifying adjectives) several conditions characterized by severe blistering. P. Vulgaris, the common variety; P. Vegetans, exuberant overgrowth of tissue in and about the bullous process; P. Foliaceus, refers to the leaf-like scaliness of superficial (subcorneal) acantholytic blisters.

Plaque - a slightly elevated lesion over 1 cm in diameter and commonly palm sized or larger. Usually consisting of an area of confluent papules. A superficial horizontal infiltration of the skin.

Pustule - a pus-filled cavity which is visible to the naked eye. May develop from vesicles (vesiculo-pustules) or bullae (purulent bullae) which contain a purulent fluid.

Scale - abnormal accumulation of or increased thickness of the horny layer. Vegetations - many small closely packed, round or pointed thread-like projections.

Pruritus - itching

Pyoderma - a generic word for a condition of the skin (derma, -dermia) that is marked by purulence (pyro-).

Seborrheic dermatitis - a common and characteristic inflammatory skin condition characterized by itching, redness and scaling of the scalp, face, chest, back and intertriginous areas.

Verruca - Latin word for warty excrescence. The plural form is verrucae.

Verruciform - an adjective meaning in the shape of warts

Verrucous - an adjective meaning full of or in the nature of (-ous) warts or roughness

Vesiculation - designates the process of formation of vesicles.