The autoimmune bullous diseases

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The immunobullous diseases are a group of acquired dermatoses that present with chronic blistering and erosions of the skin and mucous membranes. They are characterised by *in vivo* deposition of immunoreactants:

- pemphigus, where there is epidermal intercellular antibody deposition and intraepidermal blistering;
- pemphigoid, dermatitis herpetiformis (DH), linear immunoglobulin (Ig) A disease (LAD) and epidermolysis bullosa acquisita (EBA), that show basement membrane zone (BMZ) antibody deposition and subepidermal blistering.

Circulating autoantibodies can also be identified in all diseases with the exception of DH. Demonstrating these autoantibodies is of fundamental importance in the diagnosis of immunobullous diseases, and helps to exclude other skin diseases in which blistering may occur.

Recent advances in understanding the structure and molecular composition of the cutaneous BMZ have occurred in parallel with identification of target antigens for most immunobullous diseases (Fig 1; Table 1)[1]. The target antigens appear to be important in cell-to-cell or dermo-epidermal adhesion, and antibodies may cause blistering by altering or disrupting their function. Insight into the structural importance of these antigens has been gained from research in the genetically determined bullous diseases where these molecules are abnormal or absent, and from studies of 'knock-out' mice with targeted disruption of the genes coding for these molecules. Association with HLA types also shows that genetic factors influence susceptibility to immunobullous diseases.

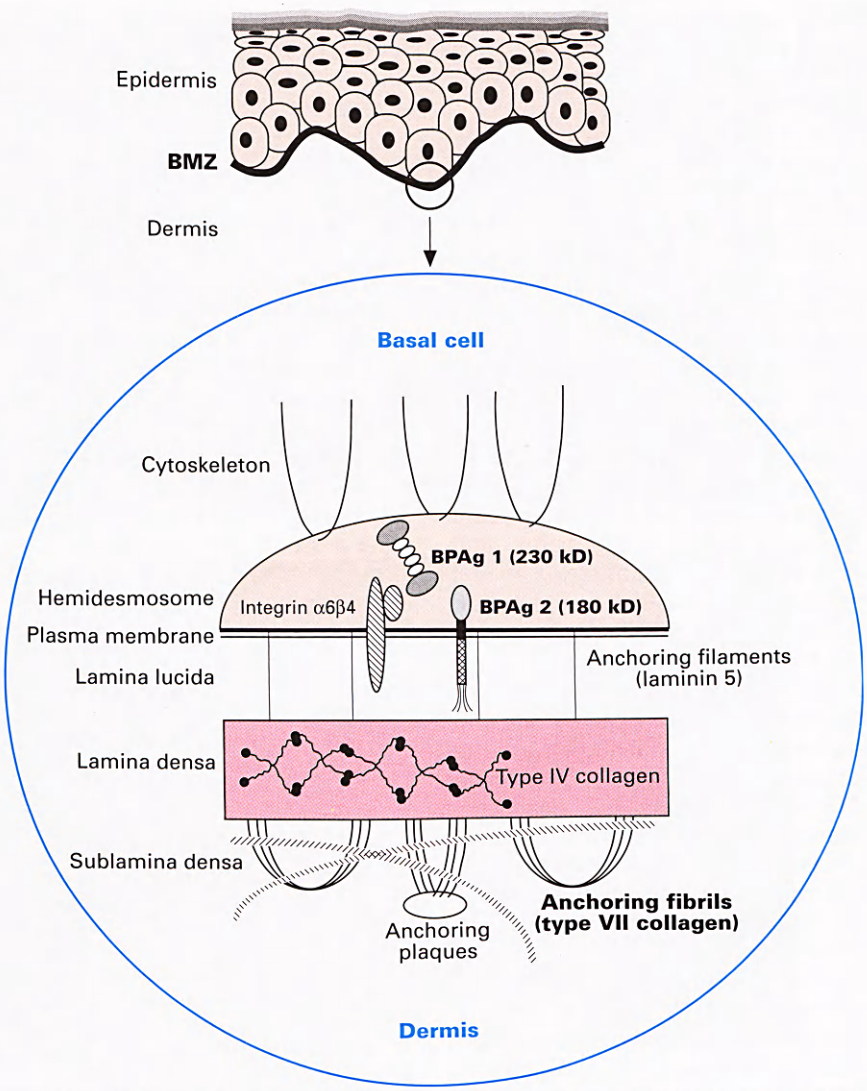


Figure 1. *Schematic diagram of the cutaneous basement membrane zone (BMZ) showing target antigens of the subepidermal immunobullous diseases* (BP = bullous pemphigoid; Ag = antigen).

Some diseases are associated with an increased risk of other autoimmune diseases, suggesting an underlying defect in immune regulation. Recent attention has focused on the role in the pathogenesis of complement (C), protease adhesion molecules and cytokines[2,3]. However, the sequence of cellular and humoral processes leading to the induction and eventual remission of immunobullous diseases is unclear. In a minority of patients, drug ingestion or infection triggers disease onset, but there is usually no obvious precipitant.

There are few epidemiological data on these diseases, all of which are rare. Geographical and racial differences have been noted. Bullous pemphigoid (BP) is the commonest immunobullous disease in Europe, with an approximate incidence of

Table 1. Immunofluorescent features of the immunobullous diseases.

Disease	Direct IMF*	Indirect IMF* – intact skin – split skin	Target antigens and localisation
Pemphigus	Intercellular IgG	Intercellular IgG	Desmosomal plaque proteins including: 130 kD Dsg3: Pemphigus vulgaris 160 kD Dsg1: Pemphigus foliaceus
Bullous pemphigoid	Linear IgG + C3 at BMZ	Linear IgG & C3 Majority epidermal binding (rarely dermal binding)	230 kD intracellular hemidesmosome protein (BP230) & 180 kD basal cell transmembrane protein (BP180)
Cicatricial pemphigoid	Linear IgG + C3 at BMZ	Linear IgG, IgA & C3 in low titre. Majority epidermal binding (rarely dermal binding)	BP230, BP180 & laminin in lower lamina lucida
Pemphigoid gestationis	Linear C3	Linear C3 binding	BP180
Linear IgA disease	Linear IgA at BMZ	Linear IgA at BMZ Epidermal binding (majority) Dermal binding (some)	Multiple BMZ polypeptides including BP230, BP180, 97 kD, 120 kD, 285 kD & collagen VII in lamina densa/sublamina densa
Dermatitis herpetiformis	Granular IgA in dermal papillae	Negative (antigliadin antibodies in serum)	Unknown
Epidermolysis bullosa acquisita	Linear IgG +/− C3 at BMZ	Linear IgG at BMZ Dermal binding	NC1 domains of collagen VII in anchoring fibrils in sublamina densa and lamina densa

*The major immunoreactants identified.

BMZ = basement membrane zone
BP = bullous pemphigoid
C = complement
Dsg = desmoglein
Ig = immunoglobulin
IMF = immunofluorescence
NC = non-collagenous

seven new cases per million per year[4], whereas pemphigus vulgaris (PV) is the commonest bullous disease encountered in the Far East.

Disease entities

Pemphigus

The pemphigus group of disorders is characterised by loss of epidermal cell cohesion (acantholysis), resulting in fragile blisters, and erosions of the skin and mucous membranes. The clinical subtypes are listed in Table 2. PV is the commonest form, accounting for 80% of all cases. It often presents with oral ulceration, which may be extensive. In all variants, cutaneous blisters rupture easily, forming large crusted erosions, and intact blisters may not be evident (Fig 2). The target antigens of PV and pemphigus foliaceus (PF) antibodies include desmogleins (Table 1), desmosomal glycoproteins which are complexed with the desmosomal plaque protein, plakoglobin, and play an important role in cell adhesion[5].

Heterogeneity in the composition of desmosomes at different levels in the epidermis may explain why blistering occurs at a suprabasal level in PV, and higher in PF[6]. Paraneoplastic pemphigus antibodies recognise multiple antigens including those derived from non-stratified epithelia, and this may represent a cross-reaction with tumour antigens. The geographical clustering of endemic Brazilian PF suggests triggering by an infective agent, possibly borne by the Simulium Black Fly.

Table 2. Subtypes of pemphigus.

- Pemphigus vulgaris:
  - Pemphigus vegetans
  - Drug-induced
- Pemphigus foliaceus:
  - Pemphigus erythematosus
  - Fogo selvagem (Brazilian endemic pemphigus)
  - Drug-induced
- Paraneoplastic pemphigus
- Immunoglobulin A pemphigus

Pemphigus antibodies produce acantholysis *in vitro* and *in vivo* after passive transfer, and transplacental passage of maternal PV antibodies may cause transient neonatal pemphigus. The circulating autoantibody titre usually correlates with disease activity in pemphigus (but not in other immunobullous diseases) and can be used to monitor therapy.

Bullous pemphigoid

BP characteristically affects the elderly, but may occur at any age including childhood. It presents with tense serous and haemorrhagic blisters and pruritic inflamed plaques (Fig 3), and often has a non-bullous prodromal phase. Two major target antigens have been identified and characterised. The BP180 antigen may be of primary importance because its immunodominant domains are extracellular and accessible to antibody binding prior to cell disruption. The pathogenicity of BP antibodies has been difficult to confirm because of species-specific

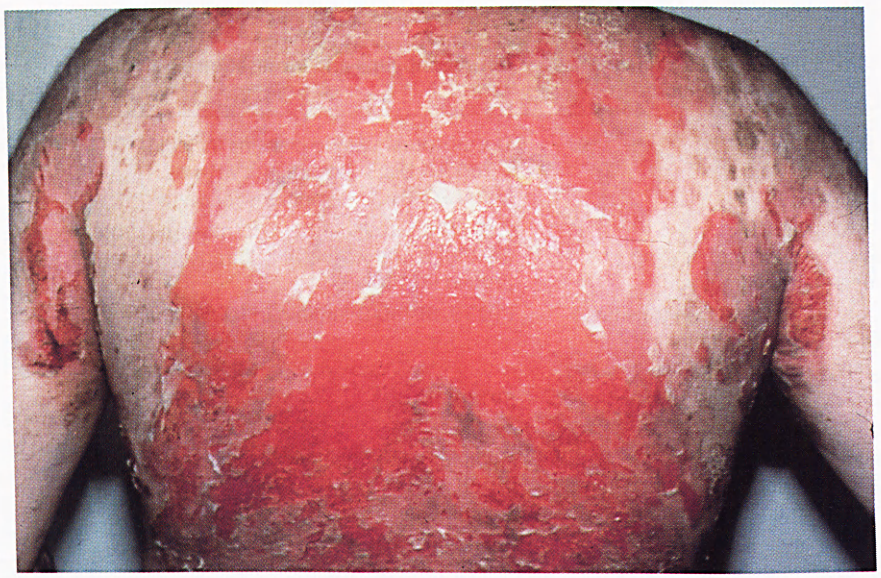
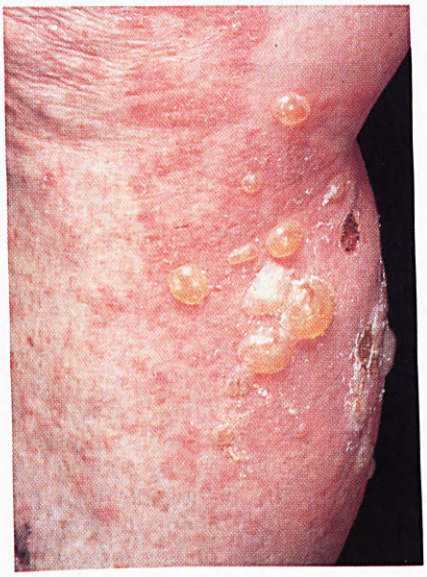


Figure 2. *Pemphigus vulgaris: widespread superficial erosions.*

differences in the major antigenic epitopes. Thus, pemphigoid can be reproduced in mice by passive transfer of antibodies raised against murine, but not against human, BP180 fusion proteins[7]. Raised levels of total IgE and BMZ-specific IgE occur in BP[8], and a shift in autoantibody subclass from IgG1 to IgG4 may play a role in the induction of remission[9].

Figure 3. *Bullous pemphigoid: tense serous blisters and urticated plaques.*



Cicatricial pemphigoid

Cicatricial pemphigoid (CP) is a chronic blistering disease that predominantly affects the mucosal surfaces. It often involves the oral mucosa, with painful deep erosions on the hard palate and desquamative gingivitis, but may be limited to the ocular mucosa (ocular CP). This disease is characterised by severe scarring (Fig 4), leading to complications such as blindness and oesophageal and tracheal strictures. The pathological mechanisms underlying this scarring are unclear, but may include fibrogenic cytokines such as transforming growth factor-β and platelet-derived growth factor released from inflammatory cells[10].

Pemphigoid gestationis

Pemphigoid gestationis (PG) is a rare autoimmune disease of pregnancy and the puerperium, which clinically resembles BP. It is characterised by bright linear deposition of C3 at the BMZ, and circulating IgG1 antibodies that have strong complement fixing ability. Transplacental passage of antibody may produce transient mild neonatal disease. Aberrant expression of major histocompatibility complex (MHC) class II antigens in the placenta appears to trigger the immune response. Cytotoxic anti-HLA antibodies against both MHC class I and class II antigens are a characteristic feature of this disease, and studies of complement polymorphisms have shown that 90% of PG cases have a C4 null allele, which may account for the abnormal handling of circulating immune complexes in this condition[11].

Linear immunoglobulin A disease

This dermatosis presents with grouped vesicles or bullae, often with symptomatic involvement of the mucous membranes such as vocal hoarseness and nasal crusting. It is defined and named after its immunofluorescence features – that is, a disease in which linear deposition of IgA class autoantibodies occurs at the cutaneous BMZ. Chronic bullous disease of childhood and LAD are now widely accepted to represent the same disease entity in different age groups[12]. Unlike DH, LAD does not respond to withdrawal of dietary gluten. Some cases are triggered by infection or the ingestion of drugs, especially vancomycin.

Dermatitis herpetiformis

DH is characterised by an intensely pruritic papulovesicular eruption, usually starting in early adult life. It is associated with a subclinical gluten-sensitive enteropathy. Both the skin disease and the enteropathy resolve on withdrawal of dietary gluten and relapse on its reintroduction, but how gluten sensitivity produces lesions at either site remains unknown. Adenoviral infection and high exposure to cereals have been proposed as triggers of the disease. Granular deposits of IgA are found within the dermal papillae in both uninvolved and clinically involved skin, and it has been suggested that these represent gluten-antigluten immune complexes. Circulating antigliadin antibodies are present in about half the patients with DH, and their presence correlates well with gut

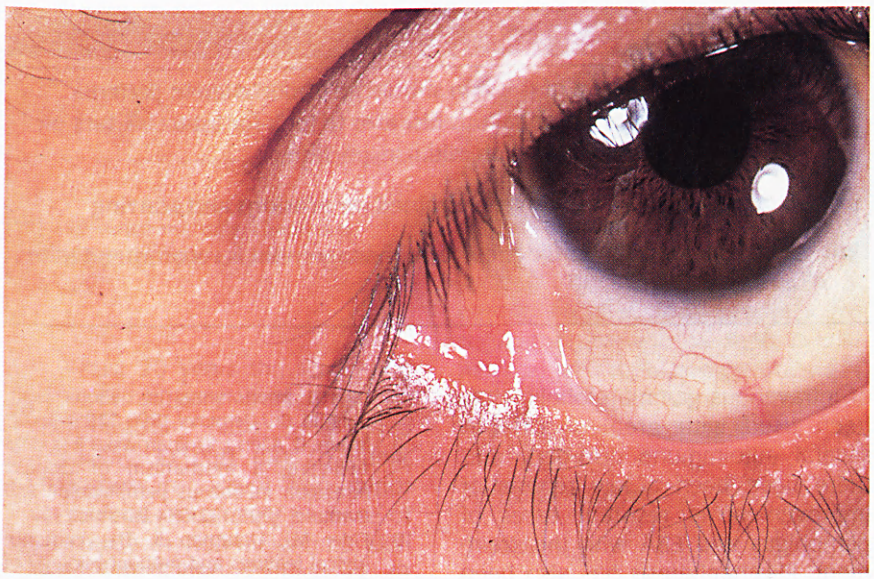


Figure 4. *Early adhesions of the ocular mucosa (symblepharon) in cicatricial pemphigoid.*

pathology. IgA antireticulin and anti-endomysium antibodies are also present in sera and gastrointestinal secretions.

The susceptibility to develop DH or coeliac disease is genetically determined, and an autosomal dominant inheritance pattern has been proposed[13]. Patients with DH are at increased risk of developing small bowel lymphomas, which is reduced by long-term adherence to a strict gluten-free diet[14].

Epidermolysis bullosa acquisita

EBA is one of the rarest bullous diseases in Europe, with an annual incidence of approximately two per 10 million[4]. It is characterised by acquired skin fragility, accompanied by blistering and scarring of trauma-prone sites which may be preceded by a BP-like inflammatory phase. There is an association with inflammatory bowel disease. The antigenic epitopes of EBA antibodies are located within anchoring fibrils in the sublamina densa zone. These sites may be important for interaction with other BMZ molecules; autoantibodies may directly impair anchoring fibril function, with consequent skin fragility. EBA shares many clinical features with dystrophic epidermolysis bullosa, in which there is a genetic abnormality in collagen VII production, and the same target antigen is recognised by antibodies in bullous systemic lupus erythematosus (SLE)[15].

EBA and bullous SLE have been reported to share a common HLA association.

Investigations

The recommended investigations for patients suspected of suffering from an autoimmune bullous disease are listed in Table 3. Some of them will be available only at specialist centres[16].

Therapy

These diseases usually run a chronic relapsing course and often require potent systemic therapy. Corticosteroids are widely used to establish disease control, but daily doses now rarely exceed 60 mg prednisolone for BP or 100 mg for pemphigus. Other immunosuppressants such as azathioprine are often used as adjuvant therapy[18,19]. Cyclophosphamide may be given in a pulsed regimen with steroids, or as a lower dose continuous therapy for pemphigus and recalcitrant BP. It has also been shown to be one of the most effective forms of treatment for

Table 3. Investigations.

Recommended investigations:

- Histology of a fresh blister – differentiates intraepidermal from subepidermal blistering
- Direct IMF of perilesional skin or mucosa – identifies the site and class of antibody deposited *in vivo* (tissue must be snap-frozen or kept in IMF transport medium)
- Indirect IMF of patient's serum on skin substrate – identifies circulating antibodies and complement fixation

Additional investigations (available in specialist centres)[16]:

- Indirect IMF of serum on 1 molar NaCl-split normal human skin*
- Direct IMF of patient's skin after splitting with 1 molar NaCl
- Western immunoblotting of patient's serum against epidermal and dermal extracts
- Immunoprecipitation of serum against protein extracts of cultured keratinocytes or fibroblasts
- Direct and indirect immunoelectronmicroscopy

* 'split skin' refers to skin that has been artificially separated through the lamina lucida of the basement membrane zone. Splitting is usually accomplished by incubation with 1 molar NaCl ('salt-split skin'). This is a more sensitive substrate than intact skin for indirect IMF in subepidermal diseases[17]. Split-skin studies also reveal whether antibodies bind to epidermal-associated and/or dermal-associated antigens (Fig 5).

IMF = immunofluorescence NaCl = sodium chloride

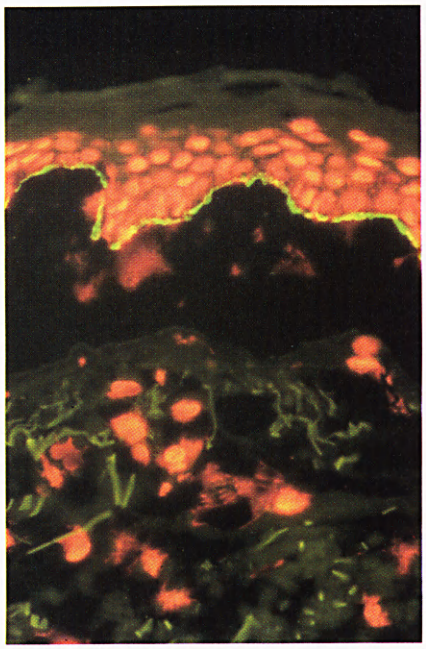


Figure 5. *Indirect immunofluorescence of bullous pemphigoid serum on salt-split human skin substrate showing immunoglobulin (Ig) G labelling to the epidermal (roof) aspect of the split. See Table 3.*

severe ocular CP. However, there are no robust studies to guide dosage regimens. These drugs may cause serious adverse effects, and they require close monitoring. Treatment may be associated with significant morbidity, especially in the elderly. A very potent topical corticosteroid alone may suffice for mild or localised BP or CP.

The IgA-mediated diseases, DH and LAD, bullous SLE and IgA pemphigus, respond to treatment with dapsone or sulphonamides. These diseases are characterised by neutrophilic infiltrates, and these drugs may act by modulating neutrophil function. A combination of tetracycline or erythromycin and niacinamide has been used as an alternative to systemic steroids in the treatment of BP, and tetracyclines alone have been used successfully in CP. Colchicine has been reported to be of benefit in a few cases of EBA, but the mechanobullous variant is often recalcitrant to therapy.

Adjuvant therapy with high doses of intravenous gamma globulins has been used with great success in several autoimmune disorders, and there have been a few reports of improvement in resistant cases of pemphigus and EBA with this treatment. Plasmapheresis has also been employed for severe disease, but must be combined with immunosuppressants to prevent rebound antibody synthesis. Other new ideas include extracorporeal photopheresis (ultraviolet irradiation of leukocytes following ingestion of psoralen). However, controlled trials of these treatments are lacking.

Key Points

- A close examination of the skin should be undertaken in patients with suspected immunobullous diseases to look for intact blisters – these may not be obvious on initial inspection
- Mucosal surfaces should be examined for erosions and scarring
- Specialist referral for diagnosis and management is recommended in all cases

References

1 Joyce Rico M. Autoimmune blistering diseases: characterization of target antigens. *Adv Dermatol* 1993;**8**:3–29.
2 Jordan RE, Kawana S, Fritz KA. Immunopathological mechanisms in pemphigus and bullous pemphigoid. *J Invest Dermatol* 1985;**85**(Suppl):72–8.
3 Wakelin SH, Wojnarowska F. Immunobullous diseases. In: Bos JD (ed). *The skin immune system*, 2nd edn. New York: Boca Raton, 1997:445–60.
4 Bernard P, Vaillant L, Labeille B, Bedane C, *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. *Arch Dermatol* 1995;**131**:48–52.
5 Amagi M. Autoantibodies against cell adhesion molecules in pemphigus. *J Dermatol* 1994;**21**:833–7.
6 Shimizu H, Masunaga T, Ishiko A, Kikuchi A, *et al.* Pemphigus vulgaris and pemphigus foliaceus sera show an inversely graded binding pattern to extracellular regions of desmosomes in different layers of human epidermis. *J Invest Dermatol* 1995;**105**:153–9.
7 Liu Z, Diaz LA, Giudice GA. Autoimmune response against the bullous pemphigoid 180 autoantigen. *Dermatology* 1994;**189**:34–7.
8 Soh H, Hosokawa H, Asada Y. IgE and its related phenomena in bullous pemphigoid. *Br J Dermatol* 1993;**128**:371–7.
9 Modre B, Allen J, Wojnarowska F. Is class switching a mechanism of disease remission in bullous pemphigoid? *Br J Dermatol* 1995;**132**:654 (abstract).
10 Elder MJ, Lightman S. The immunological features and pathophysiology of ocular cicatricial pemphigoid. *Eye* 1994;**8**:196–9.
11 Black MM. New observations on pemphigoid 'herpes' gestationis. *Dermatology* 1994;**189**(Suppl):50–1.
12 Collier PM, Wojnarowska F. Linear IgA disease and chronic bullous disease of childhood. *Eur J Dermatol* 1993;**3**:623–34.
13 Reunala T. Incidence of familial dermatitis herpetiformis. *Br J Dermatol* 1996;**134**:394–8.
14 Lewis HM, Reunala T, Garioch JJ, Leonard JN, *et al.* Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *Br J Dermatol* 1996;**135**:363–7.
15 Gammon WR, Briggaman RA. Epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. *Dermatol Clin* 1993;**11**:535–47.
16 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an update of diagnostic methods and investigations. *Clin Exp Dermatol* 1994;**19**:97–112.
17 Gammon WR, Fine J-D, Forbes M, Briggaman RA. Immunofluorescence on split skin for the detection and differentiation of basement membrane zone autoantibodies. *J Am Acad Dermatol* 1992;**27**:79–87.
18 Huigol SC, Black MM. Management of the immunobullous disorders. I. Pemphigoid. *Clin Exp Dermatol* 1995;**20**:189–201.
19 Huigol SC, Black MM. Management of the immunobullous diseases. II. Pemphigus. *Clin Exp Dermatol* 1995;**20**:283–93.

Further reading

Wojnarowska F, Briggaman RA (eds). *The management of blistering diseases.* London: Chapman and Hall Medical, 1990.