A correlation between the titre of circulating IgG autoantibodies and disease activity has been difficult to demonstrate in bullous pemphigoid. We postulate that isotype switching from "inflammatory" IgG1 to "blocking" IgG4 subclass antibodies might contribute to disease remission. We studied 16 patients with bullous pemphigoid, 3 patients with cicatricial pemphigoid and 2 patients with epidermolysis bullosa acquisita at different stages of the disease. The titres of IgG subclass and total IgG basement membrane zone autoantibodies were correlated with clinical activity. Ten of the 16 bullous pemphigoid patients went into remission. The total IgG autoantibody levels showed variable changes. IgG1 autoantibody decreased in 7 patients (3 were unchanged) and IgG4 autoantibody increased in 9 patients. The 6 patients with clinical activity did not show such changes in IgG1 and IgG4 autoantibodies. Similar results were observed with the other bullous diseases. Our data suggest that isotype switching from "inflammatory" IgG1 to "blocking" IgG4 antibody correlates with improvement in bullous pemphigoid.

Key words: subepidermal immunobullous diseases; IgG subclass; IgG1; IgG4; clinical activity.

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Bullous pemphigoid (BP) is a self-limiting autoimmune blistering disease that mainly affects elderly people. It seldom exceeds 5–6 years in duration (1–3). The target antigens for the autoantibodies are the hemidesmosome associated antigens BP230 and BP180 (4–6). Bullous pemphigoid has a clinical course that often has remissions and exacerbations. There is still a lack of predictive factors (7), although a recent paper suggests that whenever patients' sera reacted only with BP180 antigen the clinical expression was more severe and the patients were less responsive to steroid treatment (8). However, in our experience the diversity in bullous pemphigoid as regards clinical course, disease duration and prognosis is not an expression of the specificity of the target antigen (9).

Histologically, bullous pemphigoid is characterized by subepidermal blisters as a result of cleavage through the lamina lucida of the basement membrane zone (BMZ). There is a mixed dermal inflammatory infiltrate consisting of numerous eosinophils, mononuclear cells and some neutrophils (10) and on direct immunofluorescence autoantibodies and complement components are deposited along the BMZ in a linear pattern. Approximately 70% of patients with active disease have circulating IgG BMZ autoantibodies detectable by routine indirect immunofluorescence (11). No correlation between the titre of circulating autoantibodies and the severity of the disease was found in 3 studies (12–14). Our previous study showed correlation with disease activity only in some patients and did not show a change in target antigen (15). This is surprising as the autoantibodies have been shown to be pathogenic using animal models (16–18). The different inflammatory properties of the 4 IgG subclasses could account for the apparent lack of correlation between titres of IgG BMZ antibody and clinical activity. IgG1, IgG2 and IgG3 have been reported to fix complement by the classical pathway and to initiate blister formation. In contrast, the IgG4 subclass is incapable of fixing complement via the classical complement pathway and has been considered as a non-inflammatory "blocking antibody" (19–22).

We thus hypothesize that disease activity depends on the IgG BMZ antibody isotype rather than on the total IgG BMZ antibody and we postulate that antibody isotype switching from IgG1 to IgG4 should result in reduced clinical activity of the disease. The following longitudinal study on patients with bullous pemphigoid and other subepidermal immunobullous diseases was designed to test this hypothesis.

METHODS

Patients
A total of 16 patients (8 women and 8 men) with clinical, histological and immunological features of generalized bullous pemphigoid were studied (Table I). They were classified as patients showing activity and those who were in remission at the time the follow-up samples were taken 2–10 years after presentation (Table I). Remission was defined as the absence of any clinical lesions without systemic treatment. Patients with active disease had lesions on their current therapy or developed lesions when the therapy was reduced.

In addition 3 patients with cicatricial pemphigoid (CP) and 2 with epidermolysis bullosa acquisita (EBA) were observed for at least 2 years (Table II). The sera were obtained at different stages in the course of the disease. The circulating autoantibodies were correlated with the clinical activity and course of the disease to evaluate the role of the individual IgG subclasses in disease activity.

Sera
Three or four serum samples (taken for diagnosis and monitoring) at different clinical stages of the disease were obtained from each patient for up to 10 years after disease onset. The severity of the disease fluctuated markedly during this time. All serum samples were stored in small aliquots at −20°C. Sera from 8 volunteers without any clinical signs of immunobullous disease were used as negative controls. Eight sera of bullous pemphigoid patients showing the typical clinical and histological picture of the disease were taken as positive controls.

Indirect immunofluorescence
Indirect immunofluorescence was performed using our standard technique. Normal human skin was obtained from the ear of a child undergoing plastic surgery (with permission from the Central Oxford Research Ethics Committee), washed in phosphate-buffered saline (PBS) pH 7.4 and then cut into small fragments. The epidermis was separated from the dermis through the BMZ in the region of the lamina lucida by incubating for periods of 72 h in 1.0 molar sodium chloride solution at 4°C, snap frozen in liquid nitrogen and stored at −70°C. Indirect immunofluorescence on salt split skin is routinely used in our
laboratory for the differentiation and investigation of subepidermal bullous diseases and is known to enhance the sensitivity of detection of BMZ antibodies (23). Cryostat sections (6 μm) were cut from frozen blocks of split skin, put onto multiwell slides and used as substrate to determine the antibody titre in sequential sera from each of the 16 patients with bullous pemphigoid, the 3 patients with cicatricial pemphigoid and the 2 patients with epidermolysis bullosa acquisita, using a standard indirect immunofluorescence technique. The sera from each of the patients were diluted in PBS as follows: neat, 1/5, 1/10, 1/20, 1/40, 1/80, 1/160, 1/320 and 1/640. The 8 negative controls (normal human sera) and 8 positive controls (bullous pemphigoid sera) were applied at 1/10 dilution.

Total IgG BMZ antibody titre detection

A standard indirect immunofluorescence technique was employed for the detection of the total titre of circulating anti-BMZ IgG antibodies using patient sera diluted as above and fluorescein isothiocyanate (FITC)-labelled rabbit antimurine IgG at a dilution of 1/50.

IgG subclass BMZ antibody titre detection

The sera were diluted as above. The sections were incubated sequentially with patient serum, mouse monoclonal anti-human IgG1, IgG2, IgG3 and IgG4 antisera, diluted 1/100 in PBS. The monoclonal antibodies (MoAbs) were obtained from SEROTEC Laboratories, Kidlington, Oxon, UK and were highly specific for the individual IgG subclass. Finally the sections were incubated with FITC-conjugated rabbit antimouse immunoglobulins (DAKO, Denmark). The rabbit anti-mouse immunoglobulins were diluted 1/50 in PBS and were used as a secondary antibody to visualize the pattern of IgG subclass deposition.

### Table 1. Clinical, histological and immunological features of 16 patients with bullous pemphigoid and correlation of the total IgG, IgG1 and IgG4 subclasses and complement binding with disease activity

| Patient numbers | Age and sex | Histopathology | Direct immunofluorescence on intact skin | Stage of disease | Clinical picture | IgG1 | IgG4 | Total IgG | Complement |
|-----------------|-------------|----------------|-----------------------------------------|-----------------|-----------------|------|------|-----------|------------|
| Patients in remission (R) |
| No 1 | 77/F | Non specific inflammatory infiltrate | C1 | Early | + | 10 | 10 | 0 | +ve |
| No 2 | 81/F | Not done | IgG, C3 | Early | + | 80 | 0 | 0 | +ve |
| No 3 | 80/F | Subepidermal blister | IgG, C3 | Early | + | 320 | 0 | 0 | +ve |
| No 4 | 95/F | Not done | C3 | Early | + | 320 | 0 | 0 | +ve |
| No 5 | 68/M | Not done | IgG, C3 | Early | + | 320 | 0 | 320 | -ve |
| No 6 | 86/M | Oedema, inflammatory infiltrate | C3 | Early | + | 320 | 0 | 40 | -ve |
| No 7a | 84/F | Subepidermal blister | IgG, C3 | Early | + | 160 | 0 | 10 | -ve |
| No 8a | 76/F | Mixed inflammatory infiltrate | IgG, C3 | Early | + | 320 | 0 | 160 | -ve |
| No 9a | 65/F | Vesicle formation in epidermis, oedema | IgG, C3 | Early | + | 320 | 0 | 160 | -ve |
| No 10a | 89/M | Subepidermal blister | IgG, C3 | Early | + | 320 | 0 | 160 | -ve |
| Patients with continuing active disease (+) |
| No 11 | 82/M | Not done | IgG, C3 | Early | + | 40 | 0 | 10 | -ve |
| No 12 | 76/M | Subepidermal blister | C3 | Early | + | 80 | 0 | 10 | -ve |
| No 13 | 84/M | Subepidermal blister | IgG, C3 | Early | + | 80 | 0 | 80 | -ve |
| No 14 | 84/M | Not done | IgG, C3 | Early | + | 80 | 0 | 80 | -ve |
| No 15b | 57/M | Subepidermal blister | IgG, C3 | Early | + | 80 | 0 | 80 | -ve |
| No 16b | 68/F | Subepidermal blister | C3 | Early | + | 80 | 0 | 80 | -ve |

R/Remission, patient in remission with no lesions and not on systemic treatment after 2 – 10 years of disease activity.

+ patient shows significant disease activity.

a patient is in remission after 8 – 10 years with disease activity.

b patient shows disease activity after 8 – 10 years.
Table II. Total IgG, IgG1 and IgG4 subclasses and complement binding: correlation with disease activity in cicatricial pemphigoid (3 patients) and in epidermolysis bullosa acquisita (2 patients)

| Patient number | Stage of disease | Clinical picture | IgG1  | IgG4  | Total IgG | Complement |
|----------------|-----------------|------------------|-------|-------|-----------|------------|
| Cicatricial pemphigoid | No 17 | Early R | 10 | 40 | 10 | −ve |
| No 18 | Early + | 5 | 0 | Neat | −ve |
| No 19* | Early + | Neat | 10 | 10 | −ve |
| Epidermolysis bullosa acquisita | No 20 | Early + | 10 | 10 | Neat | −ve |
| No 21 | Early + | 10 | 0 | 10 | −ve |

*, patient shows disease activity.
**, patient shows more significant disease activity.
R, patient is in remission.
* patient is in remission after 8 years with disease activity.

**Complement binding detection**

Complement fixation was determined by complement immunofluorescence. Sections were sequentially incubated with patient serum, neat and diluted 1/4 in PBS, then fresh normal human serum diluted 1/5 in complement diluting buffer (as a source of complement) and finally with FITC-labelled rabbit anti-human C3 diluted 1/75 in PBS.

**RESULTS**

The results of the titres of the IgG and the IgG1, IgG4 subclasses BMZ antibody and complement binding and their correlation with clinical activity are shown in Tables I and II.

**Bullous pemphigoid patients**

The results are shown in Table I.

Ten of the 16 patients with bullous pemphigoid went into remission during the course of the study. The total IgG BMZ antibody increased in 4 of 10 patients, decreased in 3 of 10 and stayed the same in 3 of 10. IgG1 BMZ antibody decreased in 7 of 10 patients and was unaltered in 3 of 10. IgG4 BMZ antibody was increased in 9 of 10 patients and unaltered in 1 (in whom IgG1 declined). Four of 10 patients showed an increase in total IgG BMZ antibody that might reflect the shift to IgG4.

Six of 16 patients with bullous pemphigoid had disease requiring therapy throughout the study. In 4 patients the total IgG BMZ autoantibody increased, in 1 patient it stayed the same and in 1 patient the IgG autoantibody decreased. The changes in BMZ autoantibody IgG subclass levels were not clearly reflected in the total IgG. Four of the 6 patients had significant clinical activity on treatment and IgG1 BMZ antibody increased, decreased or stayed the same, in 3 patients IgG4 BMZ antibody decreased and in 1 was undetectable. Two of the 6 patients had active disease well controlled by therapy. In 1 patient both IgG4 and IgG1 BMZ antibody increased, in the other IgG4 and IgG1 BMZ antibody stayed the same. The amount of IgG1 BMZ antibody was not a reliable indicator of disease activity.

The presence of complement did not correlate with IgG1 titres, disease activity or remission (Table I).

IgG2 BMZ antibodies were found in only 3 patients, and IgG3 BMZ antibodies were not detected at all by indirect immunofluorescence.

Our data confirms that there is not always a correlation between the level of the total IgG BMZ antibody and the disease activity in patients with immunobullous diseases. Although this correlation was seen in about half of the patients (11 of 21), it was seen not in the others (10 of 21) (Table I).

**Epidermolysis bullosa acquisita patients**

The results are shown in Table II.

The increase in IgG4 BMZ antibody titres in the sera of 2 of 3 patients with cicatricial pemphigoid also reflected an improvement of the disease. In contrast no increase was found in IgG4 antibody titres in the 1 patient without clinical remission. Neither the level of the IgG1 BMZ antibody nor the level of the total IgG BMZ antibody titre correlated with disease activity. The 2 patients in remission showed a remarkable enhancement of the total IgG BMZ antibody towards the end of the disease that may reflect the shift to IgG4. In none of the patients was complement detected (Table II).

**DISCUSSION**

Our results provide an explanation for the poor correlation between disease activity and total IgG BMZ antibody in bullous pemphigoid that has been observed in some studies (12–14), a finding that seemed surprising given that the antibodies are known to be pathogenic (16–18). We believe that this is because the degree of inflammation is dependent on the IgG isotype rather than on the total IgG BMZ autoantibody.

In bullous pemphigoid a specific antigen-antibody interaction between immunoglobulins and the specific hemidesmosome-associated molecules BP180 and BP230 is thought to be the pathogenic mechanism of blister formation (4–6, 16–18, 24) and to require complement (25). The property of antibodies to fix complement leads to the activation of the classical

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pathway followed by chemotaxis of inflammatory cells, such as leukocytes, and release of proteolytic enzymes. Binding of antibodies to BMZ antigens results in damage to the BMZ, followed by blister formation through dermal-epidermal separation. The removal of pathogenic antibodies by plasmapheresis has been therapeutic (26, 27).

There are differences in the molecular structure of IgG subclasses and in their immunological functions, including the antigen specificity and the ability to bind complement. IgG4 is incapable of activating the classical pathway of complement and has been regarded as the less inflammatory “blocking” antibody (19 – 22). In the early immune response the IgG1 subclass level is usually higher than the IgG4 subclass level, but through a sequential switching process the IgG4 level may slowly increase. Isotype switching occurs in mature B lymphocytes in collaboration with helper CD4 T-cells and is cytokine dependent (28). Isotype switching from highly pathogenic IgG1 antibodies to non-complement-activating antibodies IgG4 is favourable for the host in chronic infectious and inflammatory states by reduction in the inflammatory response.

The alteration in relative proportions of IgG1 and IgG4 BMZ, with a shift from IgG1 to IgG4 autoantibodies in bullous pemphigoid that we have shown accounts for the difficulty in demonstrating a consistent correlation between disease activity and IgG BMZ autoantibody titre (12 – 14). The antibody deposition in patients in prolonged remission (11, 29) can also be explained as these might be antibodies of the IgG4 subclass, which in high amounts are protective rather than harmful.

The subclass distribution of IgG BMZ autoantibodies has been studied in bullous pemphigoid (22, 30 – 32) and other autoimmune blistering diseases (22, 33 – 38). In bullous pemphigoid IgG4 was the predominant subclass of autoantibodies (usually 4% of total serum IgG), followed by IgG1, whilst IgG3 was found only occasionally (22, 30, 32). No difference in IgG subclass distribution of bullous pemphigoid antibodies was observed during the course of the disease in a study, in which sera taken at the beginning of the disease were compared with sera taken from different patients at the end of the disease (31). The finding in these studies that IgG4 is the predominant class (22, 31, 32) contrasts with our study in which this was observed in remission but not early disease. In none of the previous studies were the individual patients and the subclass of their autoantibody response observed over a long period of time nor was there sufficient data to correlate IgG subclasses over a reasonable period of time with the disease activity (30 – 32). In our study we used highly specific monoclonal antibodies to relate the titres of IgG1, IgG2, IgG3 and IgG4 BMZ autoantibodies in the sera of 21 patients with IgG mediated subepidermal immunobullous diseases to the disease activity and the titres of IgG BMZ antibody. The best correlation with clinical activity was the change in IgG4 BMZ antibody titre rather than IgG1 or total IgG BMZ antibody titre (Table I). All bullous pemphigoid patients showed a similar IgG subclass shift with remission independent of the disease duration. The results of the cicatricial pemphigoid and epidermolysis bullosa acquisita patients broadly support this hypothesis.

In pemphigus, IgG4 was the most common subclass in patients who are in remission, whereas the IgG1 subclass was found in 100% of patients with active disease and only in 50% of those in a state of clinical remission (36). In another study on pemphigus, IgG4 was the predominant subclass and addition-ally it has been suggested that IgG1 is only present at an early stage of the disease (36). It seems likely that IgG4 has a protective role in pemphigus as well.

Our results suggest that isotype switching from highly pathogenic IgG1 antibodies to “protective” IgG4 antibodies might be one of the mechanisms contributing to remission in bullous pemphigoid and possibly also in cicatricial pemphigoid and epidermolysis bullosa acquisita.

A better understanding of immunopathological processes involving the individual immunological function of IgG subclasses might lead to the use of novel immunological therapies such as cytokines to influence B cell isotype switching. The manipulation of autoantibody isotype is promising and could contribute significantly to a more effective treatment in autoimmune blistering diseases.

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