Dapsone has been used successfully as adjuvant therapy for bullous pemphigoid (BP). The effectiveness of dapsone for this indication, however, remains controversial. We evaluated the effectiveness and adverse events of dapsone (1.0–1.5 mg/kg per day) in combination with oral methylprednisolone (tapering doses of 0.5 mg/kg per day) and topical clobetasol propionate (initially applied once daily on lesions only) in the treatment of BP. Sixty-two patients treated with this regimen were analyzed retrospectively. Patients were free of new blisters after a mean (± SD) of 22±13 days (median, 20 days). After 3 and 6 months of treatment, methylprednisolone could be reduced to less than 10 mg/d in 71% and 91% of patients, respectively; after 12 months of treatment, 53% of patients were in complete remission without receiving further therapy. Dapsone-related side effects were usually mild except in 3 patients (5%), 2 patients with anemia (hemoglobin level, <7 g/dL) and 1 with agranulocytosis. Our data suggest that dapsone used in combination with systemic and topical corticosteroids may be a relatively safe and effective treatment option for BP.


Bullous pemphigoid (BP) is an autoimmune subepidermal blistering skin disease. Systemic corticosteroids are used most commonly to suppress the formation of new blisters.1,2 The advanced age of the patients and the need for long-term immunosuppression frequently lead to severe corticosteroid-related adverse events (AEs), including death.3,4 Therefore, various corticosteroid-sparing regimens have been used in the treatment of BP, including azathioprine, dapsone, methotrexate, cyclophosphamide, cyclosporine, mycophenolate mofetil, intravenous immunoglobulin, and plasma exchange.1,2 Dapsone (4,4'-diaminodiphenylsulfone) has been advocated as first-line therapy in 4 other autoimmune subepidermal blistering disorders: dermatitis herpetiformis, linear IgA disease, mild to moderate mucous membrane pemphigoid, and childhood epidermolysis bullosa acquisita.5-9 Although good clinical responses to dapsone have been reported in BP,10,11 its effectiveness for this indication remains controversial.12-14 We retrospectively investigated the effectiveness and AEs of a regimen that included dapsone, oral methylprednisolone (at an initial dose of 0.5 mg/kg per day), and topical clobetasol propionate in 62 patients with BP.
Patients and Methods
This retrospective study included 62 patients (24 men and 38 women) treated at the Department of Dermatology, University of Würzburg, Germany, between January 1990 and December 2000. The patients’ mean (±SD) age was 72±14 years (median, 76 years). All patients had widespread bullous disease, with lesions on the arms, legs, and trunk that covered a body surface area of more than 15%. The results of direct immunofluorescence microscopy of perilesional skin biopsies revealed linear deposits of immunoglobulin G, C3, or both, at the dermal-epidermal junction in all patients. Diagnosis was based on the combination of clinical picture with extensive blistering and direct immunofluorescence microscopy. The results of indirect immunofluorescence microscopy on 1 molar sodium chloride split human skin showed that 91% of the sera labeled the epidermal side of the artificial split, and the remaining 9% were negative. Titers ranged from 1:10 to 1:1280 (median, 1:160). In 50 patients (81%), no systemic treatment had been initiated. Immediately before entering this study, the other 12 patients (19%) had been treated unsuccessfully with a combination of oral tetracycline and nicotinamide (n=11) or azathioprine (n=1) as the only oral medication. In addition, topical clobetasol propionate had been applied on all 12 patients.

After glucose-6-phosphate dehydrogenase activity was found to be within reference range in all patients, dapsone was given at a dose of 1.0 to 1.5 mg/kg per day in combination with oral methylprednisolone at an initial dose of 0.5 mg/kg per day; medication doses were related to the actual body weight of the individual patient. In addition, in the initial phase, topical clobetasol propionate 0.05% cream was applied to BP lesions once daily. Blister fluid was aspirated, and lesions were treated with 0.5% crystal violet dye. Patients also received oral doses of 150 mg ranitidin, 600 mg vitamin E, 0.025 mg cholecalciferol, and 500 mg calcium. When no new blisters had developed after one week, topical treatment was replaced with a moisturizing emollient, and methylprednisolone was tapered in 8-mg steps to 24 mg/d, then in 4-mg steps to a dose of 12 mg/d, then in 2-mg steps. When fewer than 5 new blisters had appeared in the preceding week, the methylprednisolone dose was not reduced until the patient was again blister free for one week. When 5 or more blisters were observed in the preceding week, a relapse was noted, and the corticosteroid was increased to its initial dose. After discontinuation of the systemic corticosteroid, dapsone also was tapered and usually omitted within 8 weeks if no new lesions had developed.

Patients were in complete response (CR) when no new lesions had appeared for one week and no further treatment was required, and in clinical response (CliR) when skin lesions had cleared completely for one week while the patient was still receiving treatment; partial response (PR) was defined as the appearance of fewer than 5 new blisters in the preceding week.

For statistical analysis, the Kruskal-Wallis test was applied.

Results
Effectiveness—Blister formation stopped after a mean (±SD) of 22±13 days (median, 20 days; interquartile range, 13–28 days). One week after initiation of therapy, CliR and PR rates were 11% and 45%, respectively. After 2 weeks of treatment, 32% of patients were in CliR and 49% in PR; after 4 weeks, 76% of patients were in CliR and 18% in PR. After 3 months, 98% of patients were in CliR, and the remaining 2% were in PR. After 6 months, 100% of patients were in CliR. After 3, 6, and 12 months, CR rates were 20%, 30%, and 53%, respectively (Table).

The mean (±SD) follow-up period was 108±141 weeks (median, 58 weeks; interquartile range, 20–132 weeks). The mean (±SD) duration until methylprednisolone could be reduced to less than 10 mg/d was 49±35 days (median, 39 days; interquartile range, 26–77 days). The mean (±SD) time until methylprednisolone was discontinued was 24±19 weeks (median, 18 weeks; interquartile range, 8–40 weeks), and the mean (±SD) time for discontinuation of dapsone was 37±38 weeks (median, 26 weeks; interquartile range, 8–48 weeks).

During the follow-up, 18 patients (29%) experienced a single relapse, and more than one relapse was recorded in an additional 9 patients (15%). In total, 45 relapses were noted, of which 26 (58%) were mild (≤5 new blisters).

Adverse Events—In a total of 19 patients (31%), AEs were documented as follows: anemia (hemoglobin level <7 g/dL [n=2]; ≤9 g/dL [n=2]), methemoglobinemia (>5% [n=2]), gastrointestinal disturbances (n=5), elevated serum creatinine levels (n=4), nausea (n=2), exertional dyspnea (n=4), dizziness (n=3), and exanthema (n=1). Dyspnea and dizziness were temporary, mild (did not lead to a reduction of the dapsone dose), and not accompanied by anemia or methemoglobinemia. All patients with anemia or methemoglobinemia were asymptomatic. In addition, one patient developed an agranulocytosis that was reversible after dapsone
was omitted. No case of a dapsone hypersensitivity syndrome was observed. Due to these AEs, dapsone was omitted in 5 patients (8%). In the 4 patients (6%) with elevated serum creatinine levels, dapsone and methylprednisolone were discontinued.

Five patients (8%) died within the first year after initiation of dapsone. Causes of death included heart failure (n=2), myocardial infarction, multorgan failure, and advanced age. None of these patients had anemia or methemoglobinemia.

Histopathology—Histopathology was performed in 55 patients (89%); in all patients, a subepidermal split formation was detected, accompanied by a mixed inflammatory infiltrate in the upper dermis. Of those 55 patients, infiltration of eosinophils was prominent in 33 patients (60%), neutrophils predominated in the lesions of 13 patients (24%), and a combined eosinophilic and neutrophilic infiltrate was present in 9 patients (16%). No statistically significant correlation was observed between the predominant type of inflammatory cell in BP lesions (eosinophils, neutrophils, or both) and the average time after blister formation stopped (P=.953), until methylprednisolone could be reduced to less than 10 mg/d (P=.374), and until CliR (P=.374) and CR (P=.569) were achieved.

Comment
Dapsone is thought to exhibit its anti-inflammatory effect by the suppression of various neutrophil and eosinophil functions, such as chemotaxis; adherence to endothelial cells; and the release of leukotriene B4, toxic oxygen intermediates, and proteases.16 In addition, dapsone was shown to inhibit the adherence of neutrophils to immunoglobulin bound to the basement membrane zone in patients with BP and in patients with linear immunoglobulin A disease.17 Dapsone also was shown to inhibit the release of interleukin 8 (which is a major chemoattractant for neutrophils) from cultured human keratinocytes that were treated with immunoglobulin G purified from BP sera.18 In experimental BP, the presence of neutrophils and the subsequent release of proteases are prerequisites for blister formation.19,22 Based on these in vitro data, dapsone appears to be a rational treatment option for BP.

It is thought that oral methylprednisolone at a dosage of 1.0 mg/kg per day is required to control severe BP.1,2 However, topical corticosteroids alone have been used successfully in the treatment of BP,23 and a recent study shows that high doses of topical clobetasol propionate cream (40 g/d) are more effective and have fewer AEs compared with oral methylprednisolone (1.0 mg/kg per day) in patients with extensive BP.24 In the present study, we treated 62 patients with generalized BP using oral dapsone, moderate-dose methylprednisolone (0.5 mg/kg per day), and topical clobetasol propionate. In the study by Joly et al,24 the clobetasol propionate cream was applied every day for 4 months and then every 2 to 4 days for another 8 months, requiring intensive nursing support. In contrast, our patients received the topical corticosteroid only on the BP lesions and only until the lesions had cleared (mean [±SD], 22±13 days).

No relation was observed between the type of inflammatory infiltrate in BP lesions (eosinophils, neutrophils, or both) and the effectiveness of the treatment. This result may be explained by the

### Status of Patients With Bullous Pemphigoid After 3, 6, and 12 Months of Treatment (N=62)

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>3 Months, n (%)</th>
<th>6 Months, n (%)</th>
<th>12 Months, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone reduced to &lt;10 mg/d</td>
<td>42/59 (71)</td>
<td>53/58 (91)</td>
<td>56/58 (97)</td>
</tr>
<tr>
<td>Methylprednisolone discontinued</td>
<td>20/59 (34)</td>
<td>29/58 (50)</td>
<td>35/58 (60)</td>
</tr>
<tr>
<td>Dapsone discontinued/complete response†</td>
<td>11/56 (20)</td>
<td>16/53 (30)</td>
<td>28/53 (53)</td>
</tr>
</tbody>
</table>

*After initiation of therapy. This is related to the number of surviving patients and does not include patients in whom dapsone was omitted because of adverse events.

†Defined as no blister or lesion formation for one week and no further therapy required. Note that the percentage of patients who discontinued dapsone is by definition identical to the complete response rate.
mode of action of dapsone, which inhibits the functions of not only neutrophils but also eosinophils. It has been shown, for example, that eosinophil peroxidase is more sensitive to inhibition by dapsone than neutrophil-derived myeloperoxidase.

To reduce corticosteroid-related AEs, dapsone has been introduced in the management of BP but with inconsistent results. When dapsone was given without topical corticosteroids, response rates were 46% (n = 17) and 20% (n = 15). In contrast, when dapsone was used in combination with potent topical corticosteroids, response rates increased to 63% (n = 19) and 82% (n = 17) with the exception of one study which reported only 6 responses in 41 patients with BP treated with this regimen (15%). However, in the latter study, sulfapyridine, a drug closely related to dapsone, was given. When dapsone was combined with oral prednisolone (0.5–0.75 mg/kg per day) or azathioprine, the effectiveness further increased, and CR was achieved in 12 of 13 patients. This result is consistent with our own findings, suggesting a greater effect of the combined use of dapsone plus corticosteroids compared with dapsone alone. It is hypothesized that although corticosteroids are essential in the initial phase of treatment, dapsone may be helpful to taper corticosteroids faster, to reduce the cumulative corticosteroid dose, and thus to decrease corticosteroid-related AEs. Interestingly, 12 of our patients, who had previously been treated unsuccessfully with topical clobetasol propionate either in combination with tetracycline and nicotinamide or in combination with azathioprine and methylprednisolone, responded to the regimen containing topical clobetasol propionate, methylprednisolone, and dapsone.

Dapsone-related AEs include hemolysis and methemoglobinema leading to lethargy, headache, cyanosis, tachycardia, and nausea, as well as agranulocytosis. In 19 (31%) of our patients, AEs were documented, of which 15 were most likely due to dapsone. In the 4 patients (6%) with elevated serum creatinine levels, AEs were not attributed to dapsone, because nephrotoxicity only rarely has been reported as dapsone related. In the 7 patients (11%) with dyspnea and dizziness, symptoms were temporary and mild, did not lead to a reduction in the dapsone dose, and were not accompanied by anemia or methemoglobinema. The complication rate in a study of 93 patients with extensive BP treated with topical clobetasol propionate alone was 29% (27), whereas the complication rate in 95 patients with BP treated with oral prednisolone was 54% (51). In our study, most dapsone-related AEs were mild, could usually be improved after reducing the dose, and led to the discontinuation of therapy in only 8% (5) of patients. Among these 8%, one patient had developed agranulocytosis that resolved after the discontinuation of dapsone. In dermatitis herpetiformis, agranulocytosis has been calculated to occur in 1 of 240 to 425 patients receiving dapsone and develops almost exclusively during the first 12 weeks of treatment. In our study, to minimize AEs, dapsone was combined with vitamin E to reduce hemolysis; methemoglobin and hemoglobin blood levels were monitored during the first 12 weeks of therapy, and patients were instructed to seek medical care immediately if fever developed during the first 3 months of treatment.

Interestingly, only 8% (5) of our patients died within the first year of the dapsone regimen (none of them related to the therapy). In contrast, the 1-year mortality rate was 29% of 369 patients analyzed by Rzany et al. and Joly et al. reported 1-year mortality rates of 32% of 170 patients receiving topical corticosteroids alone, 30% (23) of 76 patients treated with oral prednisolone at a dose of 0.5 mg/kg per day, and 41% (39) of 95 patients treated with oral prednisolone at a dose of 1.0 mg/kg per day. In both studies, the causes of death were not disclosed. The question whether dapsone contributes to increased survival time in patients with BP needs to be addressed in a prospective randomized trial.

Conclusion
The present study suggests that dapsone used in combination with systemic and topical corticosteroids may be relatively safe and beneficial in the treatment of BP. To further define the role of dapsone in the treatment of BP, a controlled, prospective multicenter clinical trial was initiated that compared effectiveness and side effects of oral dapsone and azathioprine, both in combination with oral methylprednisolone.

REFERENCES
4. Rzany B, Partscht K, Jung M, et al. Low serum albumin, high dosage of glucocorticosteroids, and old age are risk