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Reply

To the Editor: We are grateful to Drs. Lotti, Fabbri, and Panconesi for sharing the results of their investigations with us. Their data nicely dovetail our own studies of the pathogenesis of venous ulcers. There is now considerable evidence that the dermal pericapillary fibrin deposition observed in limbs affected by venous disease may indeed be central to the pathogenesis of this disorder.¹ Still unclear, however, are the pathogenic steps leading to fibrin deposition. Indeed, Dr. Panconesi's group provides us with further confirmation of the presence of a systemic fibrinolytic defect in patients with venous disease of the lower extremities. However, one must be careful in the interpretation of this fibrinolytic abnormality. It is not confined to patients with venous disease and can also be found in patients with systemic sclerosis or arterial insufficiency.² Yet, work in our laboratory indicates that dermal fibrin deposition does not occur in these other entities. The pathogenic steps leading to the deposition of fibrin are most likely very complex and may involve both systemic and local events. As suggested by Dr. Panconesi's group, it is hoped that further investigations of these phenomena will lead to better treatment of patients with venous ulcers. Fibrinolytic therapy, as with stanozolol, is certainly worthwhile in patients not responding to any other treatment. It is not without side effects and must be used with caution in patients with hepatic, renal, or cardiovascular disease.

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Blood eosinophilia as a severity marker for bullous pemphigoid

To the Editor: The pathogenic role of eosinophils during the initial stages of blister formation in bullous pemphigoid is suggested by several studies,¹⁻³ and a number of chemotactic and modulating factors of the eosinophils have been demonstrated in bullous pemphigoid skin lesions, including eosinophil chemotactic factor of anaphylaxis (ECF-A),⁴ histamine,⁵ C3a, and C5a. In addition, polymorphonuclear leukocytes, especially eosinophils, are necessary for in vitro experimental models of bullous pemphigoid.^{6,7} On the contrary, the clinical significance of elevated blood eosinophilia, noted by Bushkell and Jordon,⁸ has not yet been studied in this disease. In a retrospective study, we tried to demonstrate a statistical correlation between blood eosinophilia and the clinical severity of bullous pemphigoid.

During a 6-year period (1979-1984), forty-six consecutive patients, age range 50-97 (average, 78.2) with bullous pemphigoid were managed in our department. All patients had clinical, histologic (subepidermal blister), and immunologic (deposition of IgG and/or C3 along the basement membrane zone of the epidermis on direct immunofluorescence microscopy) criteria for bullous pemphigoid. Sex ratio (male/female) was 1.3. Three patients with an internal cancer (1 colonic, 1 prostatic, and 1 uterine) were excluded from the study because of the theoretical possibility of a paraneoplastic blood eosinophilia. In each patient, new blisters were counted daily before and during treatment. A white blood cell count with the percentage of eosinophils was repeated systematically at least once a week during the hospitalization period. For statistical evaluation,^{9,10} the following parameters were recorded in each patient: (1) maximal blood eosinophilia (absolute value per mm³), (2) maximal number of new daily blisters, and (3) delay (in days) of blister's clearing after systemic treatment (if done).

The average maximal blood eosinophilia was $1,403 \pm 570$ (mean $\pm$ SD) per cubic millimeter among the forty-three bullous pemphigoid patients without malignancy. Among these patients, 27/43 (62%) had a pathologic maximal blood eosinophilia (i.e., $>400/\text{mm}^3$). The maximal blood eosinophilia occurred the same day as the higher number of blisters is recorded in 49% of cases, before this day in 21%, and after this day in 30% (average delay, 4 days).

In Table I, we observe that maximal blood eosinophilia is pathologic in only 42% of patients with mild bullous pemphigoid (less than 20 new daily blisters), against 82% among patients with more extensive dis-

Table I. Relation between maximal blood eosinophilia and maximal number of new daily blisters*

Blisters		
Blood eosinophilia/mm ³	<20	≥20
<400	12	4
>400	9	18

* $\chi^2 = 7.07$; $p < 0.01$.**Table II.** Relation between maximal blood eosinophilia and delay of new blister's disappearing after treatment*

Delay (days)		
Blood eosinophilia/mm ³	<7	>7
<400	7	3
>400	7	19

* $\chi^2 = 3.93$; $p < 0.05$.

ease. The observed difference between these two percentages is statistically significant ($p < 0.01$). The non-parametric correlation coefficient between maximal blood eosinophilia and maximal number of new daily blisters is $r' = 0.589$, calculated on forty-three patients, which is statistically significant (Spearman's test; $p < 0.01$). Therefore, whatever the statistical analysis, the maximal blood eosinophilia is significantly related to the maximal number of new daily blisters in each patient.

The study of the relation between maximal blood eosinophilia and the delay of new blister's disappearing after treatment was limited to thirty-six patients without malignancy and under an effective systemic treatment (steroid alone, 6 cases; steroids + immunosuppressive drugs, 25 cases; sulfones, 3 cases; immunosuppressive drugs alone, 2 cases). In Table II we observe that if maximal blood eosinophilia is at normal levels (i.e., $<400/\text{mm}^3$), 70% of patients were controlled in less than a week, against 27% if maximal blood eosinophilia is pathologic (i.e., $>400/\text{mm}^3$). The observed difference between these two percentages is statistically significant ($p < 0.05$). Table III gives the average maximal blood eosinophilia in each of three classes separated according to the delay of new blister's disappearance after the treatment began. The average maximal blood eosinophilia differs significantly between them (non-parametric Kruskal-Wallis test; $p < 0.02$). The class-

Table III. Maximal blood eosinophilia and short-term follow-up in bullous pemphigoid

Delay of new blister's disappearing after treatment (in days)	<7	7≤	<14	≥14
Maximal blood eosinophilia (average/mm ³)	638	2,384	2,171	
Number of patients	14	8	14	

by-class analysis demonstrates that the average maximal blood eosinophilia is only statistically increased after a week's delay of new blister's disappearing (non-parametric Wilcoxon-Mann-Whitney test; $p < 0.01$). Finally, the nonparametric correlation coefficient between maximal blood eosinophilia and the delay of new blister's disappearing is $r' = 0.34$, which is just significant ($p < 0.05$; Spearman's test).

This study confirms that blood hypereosinophilia is quite common in blood eosinophilia, affecting 62.8% of our forty-three patients; this fact is in accordance with the previous results of Bushkell et al⁸ and Crotty et al,¹¹ and the average maximal blood eosinophilia is notably elevated ($1,403 \pm 570/\text{mm}^3$). More interesting is the significance of the blood eosinophilia in bullous pemphigoid. As previously described by Ahmed et al,¹² the severity of bullous pemphigoid can be estimated by the number of new daily blisters. Therefore, the significant relation between the maximal blood eosinophilia and the maximal number of new daily blisters suggests that blood eosinophilia is a marker of the severity of bullous pemphigoid. This conclusion does not depend on the retrospective character of the study because the two parameters have been recorded, in nearly all cases, before the start of the therapy.

In addition, it was interesting to determine if a raised maximal blood eosinophilia is related to a long delay of initial bullous pemphigoid control, expressed by the time of new blister's disappearing, i.e., if blood eosinophilia is a short-term prognosis indicator. This short-term prognosis depends on different factors: severity of the disease, possibility of spontaneous decrease of blisters, and, above all, the treatment modalities. In our retrospective study, despite the fact that maximal blood eosinophilia precedes in nearly all cases start of the treatment, the heterogeneity of these makes a final conclusion difficult. The results, concerning the relation between maximal blood eosinophilia and the blister's disappearing delay, although statistically significant, are only given as indicatives. Finally, this relation, if demonstrated on randomized prospective studies, is

very interesting because of low cost and wide availability of blood eosinophilia counts as compared with indirect immunofluorescence of bullous pemphigoid, which is not as reliable as in pemphigus vulgaris.

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Juvenile hyaline fibromatosis

To the Editor: Juvenile hyaline fibromatosis is a rare form of fibromatous proliferation occurring in children. It has well-defined clinical, microscopic, and ultrastruc-

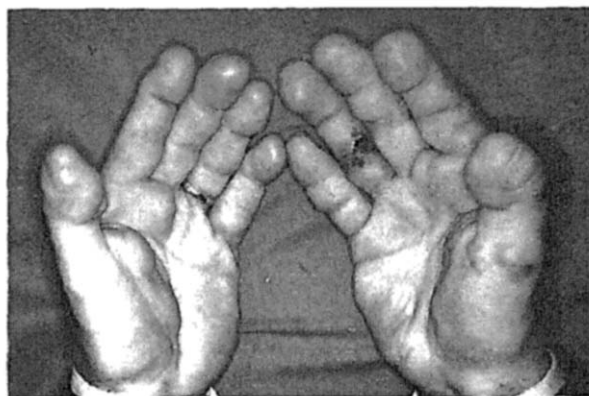


Fig. 1. Multiple subcutaneous nodules on both hands.

tural features. However, little is known about the natural history and complications of this disease. We studied its clinical course in a 51-year-old man, representing the longest survival reported to date.

Case report. A 51-year-old man was referred to our hospital for evaluation of multiple subcutaneous nodules. Symptoms were first noted at the age of 6 years and consisted of a parieto-occipital, painless tumor that was excised on various occasions and reappeared. At the age of 24, an attack of pain and stiffness caused hip disability. At the same time the patient experienced severe arthralgias in both knees, and subcutaneous tumors appeared on the scalp, shoulders, arms, and elbows. Since the age of 30, involvement of coxofemoral, femorotibial, and scapulohumeral joints progressed. New subcutaneous nodules were visible on both palms and fingers. Most recently, temporomandibular disease interfered with mastication; an oral mucosal tumor and painless falling out of three molars during a year were also observed.

Physical examination revealed subcutaneous translucent nodules and deep tumors of rubbery consistency (Fig. 1), from 3 to 6 cm in diameter, located on the palms, metacarpophalangeal, interphalangeal, and distal phalangeal regions, scalp, hips, elbows, and oral mucosa. Clubbing of the fingers was noteworthy. Tumors caused joint motion impairment and marked deformities. Limited joint motion of the coxofemoral, femorotibial, scapulohumeral, and temporomandibular joints was especially evident. Results of routine laboratory tests were within normal limits. Rheumatoid factor was negative. Chest x-ray examination was normal. Marked osteolysis of the distal phalanges of the fingers was seen on a skeletal survey (Fig. 2).

Pathologic findings. The specimen from previous biopsies and a newly obtained biopsy specimen from a nodule on the hand were available for histopathologic study. The tumors were located in the reticular dermis and subcutaneous tissue, being separated from the epidermis by a wide grenz zone. They consisted of cords of spindle cells surrounded by a dense, homogenous hyaline stroma (Fig. 3). The tumor cells showed an artifactual peripheral clear halo and were uniform