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The Analgesic Effect of EMLA Cream on Facial Skin

Quantitative Evaluation Using Argon Laser Stimulation

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The hypoalgesic effect of EMLA cream (Eutectic Mixture of Local Anesthetics) applied for 5, 15, and 30 min on facial skin was evaluated. Hypoalgesia was assessed by changes in pain thresholds to brief argon laser stimuli 0, 2, 5, 10, 15, 20, 25, 30, 45, and 60 min after removal of EMLA cream. The local cutaneous vascular changes induced by EMLA cream was evaluated by Erythema Index determined by reflectance spectroscopy and by laser Doppler blood flowmetry. A large inter-individual variability in analgesic efficacy was observed. The volunteers could be divided into two groups, one group of 6 persons where EMLA induced analgesia or considerable hypoalgesia, and one group of 4 persons where EMLA had no or only slight hypoalgesic effect. This great variability should be considered when EMLA cream is used for facial application in the clinic. Differences in local blood flow probably contribute to the variability. Application of EMLA cream for 5 and 15 min did not change erythema of the skin, while 30 min of application caused minor blanching. ***Key words: Facial application; Pain threshold.***

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EMLA cream (Eutectic Mixture of Local Anesthetics) is used prior to venepuncture (1, 2) and to provide analgesia for various painful dermatological procedures (3). Successful use of EMLA cream has been reported for e.g. laser treatment of condyloma acuminata (4), laser treatment of portwine stains (5, 6), cutting of split skin grafts (7), and curettage of molluscum contagiosum (8, 9).

The application time recommended to provide sufficient analgesia on intact skin is a minimum of 60 to 90 min (3), often with a delayed effect after removal of the cream from the skin surface (10). To obtain analgesia on genital mucosa, only 5–15 min of application is needed (4, 11, 12). In a previous study (13) we used laser stimulation to evaluate the analgesic efficacy of EMLA cream applied for 30 to 120 min on the forehead and cheek, the back, the cubital fossa and the dorsum of the hand. We found that on facial skin only hypoalgesia was observed for a short period after the EMLA cream had been removed. This was different from the effects of EMLA cream observed in the other regions, where total analgesia can be obtained for 60 to 180 min. The aim of the present study was to further evaluate the anesthetic effect of EMLA cream on facial skin for short application times. As infiltration of anesthetics in the facial region is painful, EMLA cream application would be a useful alternative, if adequate analgesia can be obtained. Two questions were formulated: 1) Can analgesia be obtained on facial skin using EMLA cream? and 2) What is the most adequate application time?

MATERIAL AND METHODS

Volunteers

Ten healthy volunteers, 5 females (mean age 36 years, range 23–52 years) and 5 males (mean age 27 years, range 23–30 years) participated. All volunteers gave their informed consent. The study was carried out in accordance with the Declaration of Helsinki. The study was approved by the regional Scientific-Ethics Committee and by the National Board of Health. No analgetics or alcohol was allowed 48 h before each trial.

Determination of pain thresholds to brief argon laser pulses

The output from an argon laser (Model 168, Spectra Physics, USA) was transmitted to the skin via a quartz fibre. The wavelengths were 488 nm (blue) and 515 nm (green). Output power could be adjusted from 50 mW to 3.5 W. An external laser power meter (Ophir, Israel) was used to measure the dissipated output power at the skin level. A continuous, low-energy beam (50 mW) from the laser was used to visualize the stimulation site. The laser stimulus had a duration of 200 ms and the laser beam diameter was kept constant at 3 mm. The pain threshold was defined as a distinct pricking pain. The threshold was calculated as a mean of five ascending and five descending series of stimulations (10, 14, 15). The volunteers wore protective goggles and rested comfortably during the measurements.

The highest laser intensity used was 3.0 W, because higher intensities could cause minor burn lesions. Where pain thresholds were higher than 3.0 W (no distinct pricking pain sensation, when laser pulses of 3.0 W were applied to the skin), pain thresholds were defined to 3.0 W.

Application of EMLA cream

EMLA cream (AB Astra, Sweden) is an oil-in-water emulsion (3). The oily phase consists of an eutectic mixture of lidocaine (25 mg/ml) and prilocaine (25 mg/ml). Two and a half grams of EMLA cream was applied on encircled (approximately 7 cm^2) test areas on the forehead. The cream was applied under an impermeable plastic occlusion (Tegaderm, 3M, UK) for 5, 15, or 30 min.

Erythema measurement

Erythema Index was measured by reflectance spectroscopy (16) before application of EMLA cream and 5, 20, 40, and 60 min after removal of EMLA. Erythema Index is a measure of the blood content in the upper dermis and is given in arbitrary units.

Blood flow

Cutaneous blood flow was measured by laser Doppler flowmetry (Periflux, Perimed, Sweden) before application of EMLA and 5 min after removal of EMLA cream.

Statistics

Two-sided Wilcoxon's rank sum test was used for statistical analysis, and statistical significance was assumed at the 5% level. Pain thresholds determined after removal of EMLA cream were compared to pre-application thresholds.

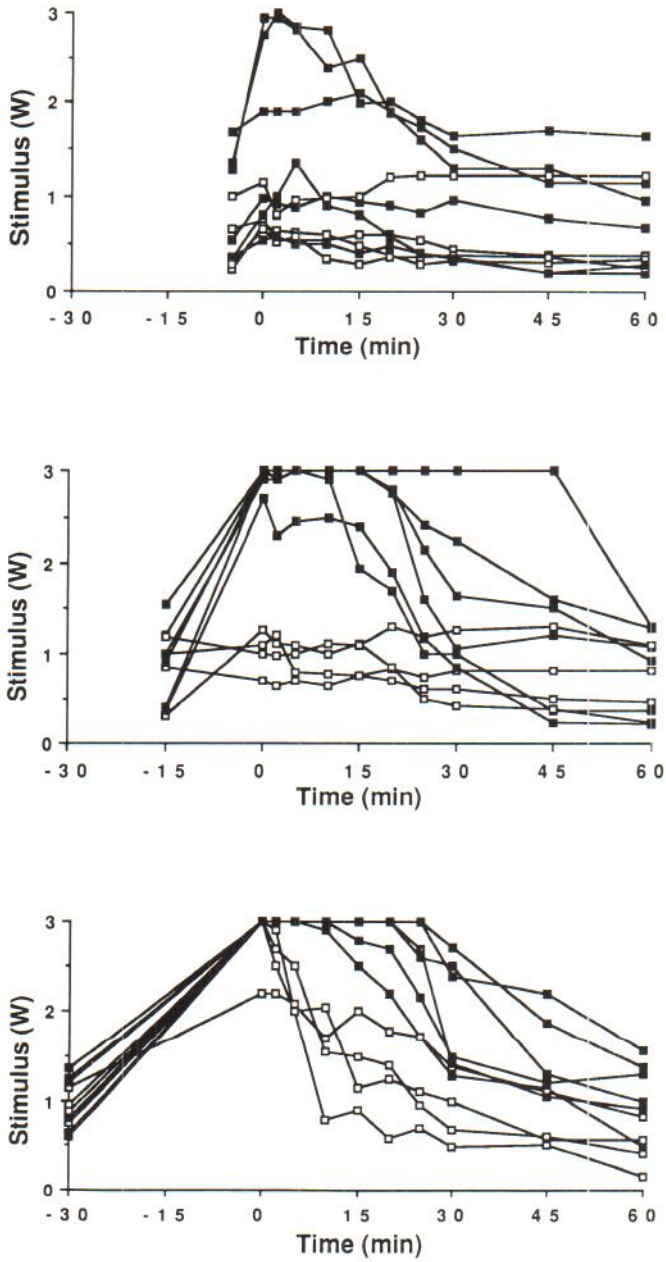

Fig. 1. Pain thresholds (W) before application and after removal of EMLA cream applied for 5 min (upper), 15 min (middle), and 30 min (lower) of each of the 10 volunteers. Individual curves are shown. The volunteers could be divided into two groups, one group of 6 persons where EMLA induced analgesia or considerable hypoalgesia (■), and one group of 4 persons where EMLA induced no or only slight hypoalgesia (□).

Protocol

Each volunteer was tested three times in a randomized cross-over design. The three tests corresponded to the three application times of 5, 15, and 30 min. One week elapsed between each trial. The application time was randomized between the three trials. Pain thresholds were measured before application, immediately after, and 2, 5, 10, 15, 20, 25, 30, 45, and 60 min after removal of EMLA cream.

Table I. *Erythema Index measured by reflectance spectroscopy before application and after removal of EMLA cream applied for 5, 15, and 30 min. Arbitrary units. Mean values and (SD) are shown. No significant differences from pre-application values were found*

EMLA application time	Before EMLA	After 5 min	After 20 min	After 40 min	After 60 min
5 min	15.4 (2.6)	15.0 (2.8)	15.6 (1.9)	15.9 (2.1)	16.7 (1.8)
15 min	15.4 (2.6)	14.9 (3.2)	14.6 (2.7)	15.5 (4.0)	16.6 (2.3)
30 min	15.4 (2.6)	13.3 (3.1)	14.2 (2.0)	14.3 (1.4)	14.9 (2.8)

RESULTS

Pain thresholds

Pain thresholds following application of EMLA cream for 5, 15, and 30 min are shown in Fig. 1. Obviously, the mean hypoalgesic effect increases with increasing application time (Fig. 1).

Apparently, the 10 participants can be divided into two groups (Fig. 1). One group of 4 persons, where application of EMLA cream for 5 or 15 min induced no hypoalgesia, and where duration of hypoalgesia following 30 min of EMLA application was very brief. In this group, 30 min of EMLA application induced analgesia in 3 volunteers immediately after removal of EMLA cream, but only hypoalgesia was observed 2 min after removal. The other group consists of 6 persons. In this group hypoalgesia was observed in 4 volunteers after application of EMLA cream for only 5 min. Following 15 min of EMLA application, longer lasting analgesia – 15 min or more – was observed in 4 persons, and considerable hypoalgesia was observed in the last 2 persons. Following 30 min of EMLA application, analgesia was observed for 5 – 25 min after removal of EMLA cream in the second group. Fifteen minutes of application of EMLA cream (Fig. 1) clearly divides the two groups.

The group of 6 where EMLA induced considerable hypoalgesia or analgesia consisted of 4 males and 2 females, and the mean age was 31 years (range 23–52 years). The group of 4 where EMLA had only slight effect consisted of one male and 3 females, and the mean age was 32 years (range 26–43 years). There were no conspicuous differences in skin colour or skin type between the two groups.

Table II. *Blood flow measured 5 min after removal of EMLA cream applied for 5, 15, and 30 min using laser Doppler flowmetry. Arbitrary units. Mean values and ranges are shown. No significant differences were observed*

Blood flow	EMLA applied for		
	5 min	15 min	30 min
Mean	6.6	5.5	5.1
Range	3.6–14.2	1.9–13.1	2.1–12.7

Erythema Index

No differences in erythema from pre-application values were observed after 5, 15, or 30 min of application (Table I). After 30 min of application of EMLA, we observed a decrease in erythema index relative to the pre-application value, indicating blanching. The difference was not significant ($0.05<p<0.10$).

Cutaneous blood flow

The overall mean cutaneous blood flow before application of EMLA cream was 3.76 (SD: 0.98). The mean cutaneous blood flow 5 min after removal of EMLA cream decreases with increasing application time of EMLA (Table II). The difference is not significant. The inter-individual variability is very large.

Cutaneous blood flow and analgesic efficacy

The cutaneous blood flow after removal of EMLA cream applied for 15 min was substantially larger (mean 8.4, range 5.6 – 13.1) in the group of 4 persons where EMLA had no or slight effect, than in the group of 6 persons (mean 3.6, range 1.9–5.8), where the effect of EMLA was quite good. No noticeable differences in blood flow between the two groups were observed after application of EMLA for 5 or 30 min.

DISCUSSION

The results of the present study demonstrate a large inter-individual variability in the analgesic/hypoalgesic efficacy of EMLA cream on facial skin. Such inter-individual variability in response to EMLA analgesia has not previously been reported. Interestingly, local analgesia can be obtained on facial skin in some patients by EMLA, and for a duration sufficient for minor surgical procedures.

The large inter-individual differences in analgesic effect and duration of effect after application of EMLA cream on facial skin (Fig. 1) are probably due to inter-individual variations in local blood flow and local epidermal and dermal thickness. We found that the local, cutaneous blood flow after removal of EMLA (applied for 15 min) was higher in the group where EMLA cream had only slight effect than in the group where EMLA had considerable hypoalgesic effect. When the cutaneous blood flow is high, the vascular uptake of analgesics is high, and the analgesics are probably washed away from the local connective tissue around the nerve endings, resulting in more brief and subtotal analgesia. Previously we (13) have demonstrated that the mean cutaneous blood flow on the forehead and cheek is significantly higher than the cutaneous blood flow on the back, the cubital fossa and the dorsum of the hand, and that blood flow correlates to local efficacy of EMLA cream. This is also in accordance with the findings of Juhlin et al. (17), who demonstrated that EMLA cream is absorbed more rapidly from intact facial skin than from intact skin on the forearm, and that EMLA cream is absorbed more rapidly from diseased skin, where the local cutaneous blood flow is higher than normal, e.g. atopic dermatitis and psoriasis. Moreover, inter-individual variations in the composition of connective tissue in local subcutis and cutaneous vessels might contribute to the differences in analgesia. Arendt-Nielsen et al. (18) demonstrated no effect of EMLA in patients with Ehlers Danlos syndrome, a hereditary connective tissue disorder.

The great variability in hypoalgesic response between volunteers observed after 15 min of application of EMLA cream on facial skin was reduced after 30 min of application of EMLA (Fig. 1). This is in accordance with the findings of Juhlin and Evers (3), who found that the great variability in response between volunteers subjected to shorter application times is decreased if longer application times are used, when EMLA cream is applied to the skin of the lower arms.

The present findings of a non-significant decrease in Erythema Index and a minor decrease in local cutaneous blood flow with increasing application time of EMLA indicate a slight blanching reaction after 30 min of EMLA application. This is in accordance with previous results (16,19). In the study performed by Bjerring et al. (16), the Erythema Index was significantly ($p=0.05$) reduced from the pre-application value immediately after 30 min of EMLA application on the forearms, and the maximum reduction in Erythema Index was seen after application of EMLA for 90 min. The present study demonstrates that blanching cannot be detected when EMLA cream is left on facial skin for only 5–15 min.

EMLA cream is used for different painful procedures on facial skin, e.g. curettage of molluscum contagiosum (8, 9), laser treatment of portwine stains (5, 6), manipulation of the fractured nose (20), and management of painful otitis externa (21). Following the results of the present study, the degree of hypoalgesia induced by facial application of EMLA should be tested e.g. by a forceps or a needle prior to surgery. If insufficient analgesia is obtained, supplemental infiltration of a local anesthetic could be provided. This procedure is suggested for children and patients undergoing repeated facial surgery or laser treatments.

EMLA cream applied for 30 min on facial skin had a brief hypoalgesic effect also in the group of persons where longer lasting analgesia/hypoalgesia was not obtained. This would probably enable a clinician to carry out a very short procedure painlessly in this group.

Generally, an application time of EMLA cream of at least 60 min on intact non-facial skin has been proposed (3, 5, 7, 9). Recently it has been reported that application of EMLA cream for 5 min reduces the pain associated with antecubital venepuncture (22). The present study indicates that a 30 min application time of EMLA cream on facial skin is sufficient to provide analgesia for most procedures in those patients where EMLA can induce analgesia.

In conclusion, the inter-individual variation in hypoalgesic effect induced by EMLA cream on facial skin is large and should be considered when EMLA cream is used clinically in this region.

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Topical Ketoconazole does not Potentiate Oral Cyclosporin A in Allergic Contact Dermatitis

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Cyclosporin A is an effective drug but its use is limited by its side effects. Since oral ketoconazole inhibits the metabolism of oral cyclosporin, we set out to find out whether topical ketoconazole would enhance the effect in the skin of oral cyclosporin. Five patients with contact allergic dermatitis (CAD) were given a 6-day course of cyclosporin (1 mg/kg/day) and applied 2% ketoconazole cream to an area on one arm and the inert base to the other. Serial dilutions of the relevant allergen were aplied to the arms at 3 days for 48 hours, and the responses were measured objectively a day later. There was no significant difference between responses at the two sites, indicating that topical ketoconazole does not enable the dose of oral cyclosporin to be reduced in CAD.

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Cyclosporin A is a very effective treatment for many skin disorders including allergic contact dermatitis (1), but its oral use is limited by dose-related unwanted effects, particularly nephrotoxicity, and it has been ineffective topically, presumably because of poor penetration. Cyclosporin is metabolised in the liver by the microsomal mixed function mono-oxygenase system, which can be inhibited by oral ketoconazole (2). Since this enzyme system is also active in the skin (3), we wondered whether its inhibition by topical ketoconazole, which has been shown to penetrate the epidermis (4), would enhance the concentration of cyclosporin in the skin and allow a greater effect from a lower oral dose. We therefore set out to study whether topical ketoconazole would enhance the effect of oral cyclosporin on the allergic contact dermatitis reaction.

MATERIALS AND METHODS

Five patients with contact allergic dermatitis and a positive response using conventional patch testing to one of a variety of common allergens (including nickel, chromate, and thiurams) were studied, using our quantitative method for patch testing to dilutions of common allergens (5). Patients were commenced on a 6-day course of 1 mg/kg/day of cyclosporin A and given 2% ketoconazole cream to apply twice daily to an outlined area on one upper inner arm and inert cream to a symmetrical area on the other arm for 72 h in a single blind design. The dose of 1 mg/kg/day was chosen because we have shown that this suppresses the contact dermatitis response only partially (1). We measured patch test responses quantitatively as previously described (5), using four doubling dilutions of the allergen as supplied for routine patch testing (Trolab) which were made in white soft paraffin and loaded in 5 ml syringes. At 72 h a 5 mm length of allergen of each concentration was applied to a Finn chamber on Scanpor adhesive (Epitest Ltd) and placed symmetrically on both arms within the areas to which ketoconazole or placebo had been applied. The patches were removed after 48 h, and 24 h later the responses were measured as change in skin thickness using Harpenden callipers with one spring removed (6). Results were analysed by analysis of variance.

In eight control patients who were not given oral cyclosporin, patches were applied as above.

RESULTS

We have previously shown a good correspondence between the measured reaction and clinical assessment of response (5). The size of the response to common contact allergens measured as skin thickness showed a direct relationship to the dose of allergen applied ($p < 0.05$). There was no significant difference between the size of the responses at each concentration at sites to which ketoconazole had been applied and sites to which inert cream had been applied. In the eight control patients there was no difference between the ketoconazole- and the placebo-treated sites.

DISCUSSION

Our present findings are in keeping with our previous observation that whereas cyclosporin at a dose of 2.5 mg/kg/day almost completely inhibits the contact allergic response to topically applied allergens (1), at doses of 1 mg/kg/day responses occurred to a range of doses of allergen. Thus topical ketoconazole did not enhance the inhibitory effect of cyclosporin on contact allergic responses, although the dose of cyclosporin we chose would have allowed its detection. We therefore conclude that metabolism of cyclosporin by mixed function mono-oxygenases in human skin is not critical to its effects on the skin, which could be because either the specific sub-group of enzymes responsible for the metabolism of cyclosporin is not present to a significant level in the skin or because cyclosporin has a central, and not a peripheral site of action. Concomitant administration of topical ketoconazole does not permit a reduction in the dose of oral cyclosporin for the treatment of skin disease.

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A New Kind of Skin Lesion in Behçet's Disease: Extragenital Ulcerations

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A new skin lesion was encountered in 29 of 970 Behçet's patients. The lesions resembled oral aphthae clinically, were recurrent and left a scar tissue like genital ulcers but were located extragenitally. Skin biopsies could be done in only 4 cases and they all showed vasculitis.

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Behçet's disease was first defined by Dr. Hulusi Behçet (1) as a trisymptom syndrome which manifested itself with aphthae in the mouth, genital ulcerations and iridocyclitis with hypopyon. Later, other features have been added to the clinical picture of this syndrome including skin changes, joint involvement, obstruction of arteries or veins and infection of sterile injection sites (2–5). Current research holds that the basic pathological disorder in Behçet's disease is vasculitis (6, 7). The aim of this report was to present a different type of skin lesion not defined before that was encountered in 29 of 970 patients who were followed at our Behçet's Disease outpatient clinic of the Department of Dermatology of Istanbul Medical Faculty.

MATERIALS AND METHODS

Nine hundred and seventy registered Behçet's outpatients were followed at regular intervals for 2 years. Recurrent extragenital ulcerations were observed in 29 of them (2.9%). Twelve were male, 17 female and the mean age was 34 in both sexes.

RESULTS

Clinical symptoms in the 29 patients with recurrent extragenital ulcerations are summarized in Fig. 1. These lesions resembling the aphthae were sharply demarcated with a bright red areola and were formed on greyish white bases. Generally they healed in 7–10 days except one which took one month to disappear. All the lesions healed with scarring like genital ulcerations.

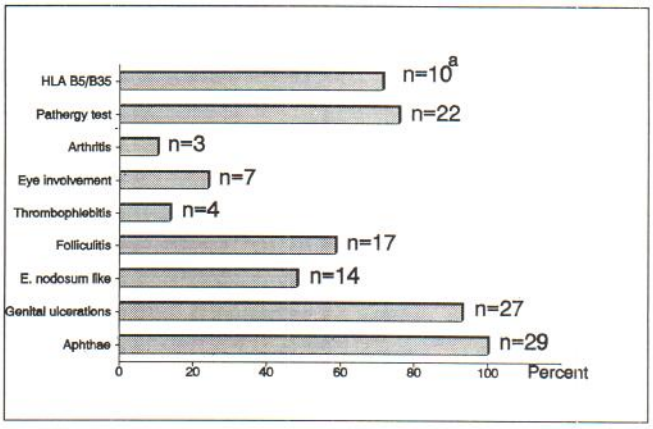

Fig. 1. Clinical symptoms in 29 patients with Behçet's disease.
[a] HLA B5 was done in 14 patients.

The locations of the lesions were as follows: On breaths in 7 female patients, on legs (especially on the back) in 10 female and 6 male patients, on axillae in 1 female and 2 male patients, on interdigital skin of the foot in 1 female and 2 male patients, on inguinal regions in 2 female and 3 male patients. Five patients showed more than one dermal location at the same time. Skin biopsies could be done in 4 cases and they all showed vasculitis.

DISCUSSION

Folliculitis resulting in necrosis and lesions resembling pyoderma gangrenosum or Sweet's syndrome have all been described in Behçet's disease (8, 9). There is no report commenting on extragenital ulcerations in the literature. Of the 29 patients, 1 female patient had an ulceration on the breast skin as the first lesion of her disease and we have not found any reports on a similar case. We believe that these recurrent, extragenital, aphthae-like lesions that heal with scarring like genital ulcerations represent a new kind of infrequently encountered skin lesion of Behçet's disease not previously reported.

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Extraskeletal Osteochondroma in the Finger

Mimicking the Fourth Phalangeal Bone

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A 36-year-old Japanese woman with an extraskeletal osteochondroma in the left thumb is reported. A roentgenogram showed a calcified tumor, located at the distal portion of the left distal phalanx, which mimicked the fourth phalangeal bone. The pathogenesis might in this case be hamartomatous.

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Although a considerable amount of data has been accumulated on cartilaginous tumors attached to or arising from bone and/or cartilage, much less information is available on the various soft tissue tumors. Extraskeletal chondroma is usually solitary, dome shaped, bony hard, and is found most commonly in the distal extremities, especially in the fingers. To date only twelve cases have been reported in Japanese. In this study we describe a solitary, white, bony hard nodule in the thumb of a Japanese woman.

CASE REPORT

A 36-year-old Japanese woman presented with a hard mass protruding at the tip of the left thumb. The tumor had been slowly growing in size for three years. Physical examination revealed an 8 mm by 11 mm white, hard tumor with a smooth surface (Fig. 1). A roentgenogram showed a calcified tumor, located at the distal portion of the left distal phalanx. There was no evidence of bone involvement (Fig. 2). Routine laboratory tests revealed normal results: blood cell count, liver function, blood chemistry, serum electrolytes, and parathyroid hormone.

Under digital block anesthesia with lidocaine, the overlying skin was completely excised. The calcified mass was then easily separated from the surrounding tissues. Histological findings revealed that a round cartilaginous nodule was situated in the dermis, deep in the tip portion of the distal phalangeal bone, between ventral corium and the dorsal subungual corium of the skin. It consisted of a sharply demarcated, mature hyaline cartilage that changed gradually into cancellous bone and which was more pronounced at the center than at the periphery of the tumor lobule. Bone marrow inside the cancellous bone was devoid of hematopoietic cell-lines (Figs. 3 and 4).

DISCUSSION

Osteochondroma is a benign neoplasm that arises most commonly at or near the ends of long bones. The occurrence of osteochondroma in soft tissue is however rare. Chung & Enzinger (1) employed the term soft part or extraskeletal chondroma for small and well-defined solitary nodules of hyaline cartilage that are unattached to bone and occur primarily in the distal extremities, especially in the fingers and the hand.

Dahlin & Salvador (2) insisted that virtually all of their series of cartilaginous tumors of the hands or feet were of synovial origin. Chung & Enzinger (1) pointed out that all the tumors in their series, manifested as a solitary nodule, were closely associated with a tendon sheath, joint capsule, or periosteum. In our case, however, no synovial tissue was identified histologically. The reported recurrence rate varies from 5% (3) to 18% (1), so careful clinical follow-up is important.

Two points are of note in this case: (1) Site and shape took the position of extruding "phalanx distalis" of the left thumb, which does not normally exist except as an anlage or a vestige. (2) Histological findings show an organic composition, general similar to the phalangeal bone, although the articulate position between the two phalanges was unclear. As no previous trauma had been reported the tumor might in this case have a hamartomatous pathogenesis.

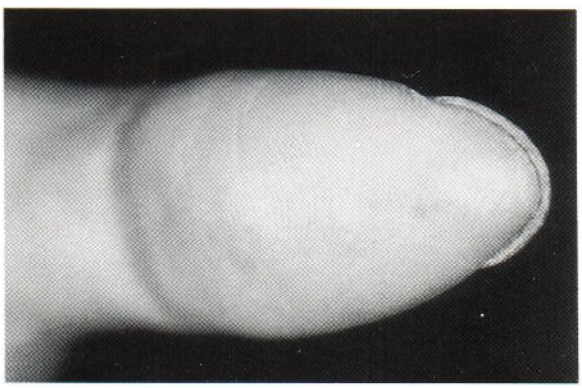

Fig. 1. A white tumor protruding at the tip of the left thumb.

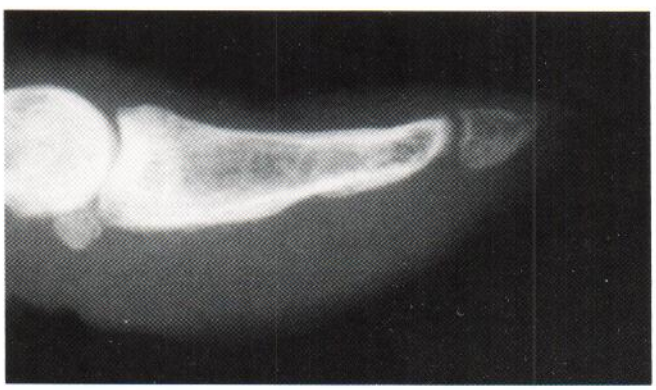

Fig. 2. Roentgenogram of the thumb.

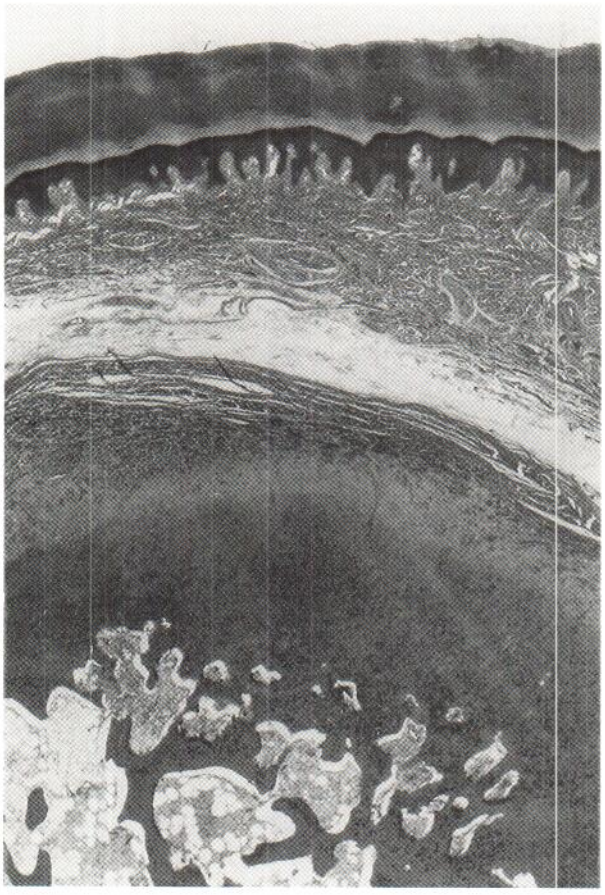

Fig. 3. Mature hyaline cartilage and cancellous bone formation into the center (Hematoxylin-eosin stain, ×66).

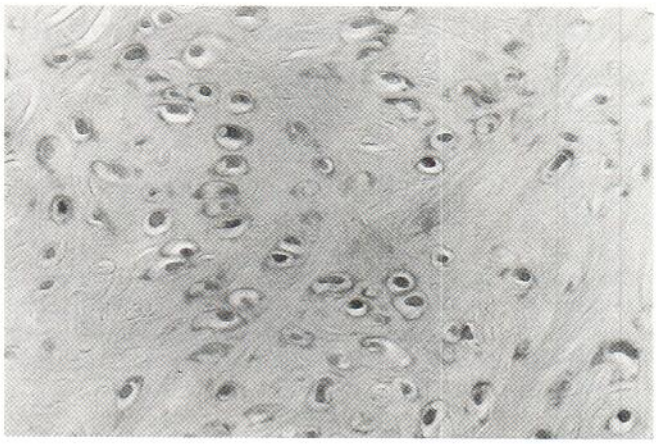

Fig. 4. Middle magnification shows mature hyaline cartilaginous cells (Hematoxylin-eosin stain, ×100).

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Rheumatoid Arthritis: An Association with Pemphigus Foliaceous

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We have observed a high incidence of pemphigus foliaceous, in the absence of therapy with penicillamine, within a small population of patients with rheumatoid arthritis. We suggest that penicillamine as well as inducing autoimmune disease might exacerbate subclinical pemphigus foliaceous in this group, accounting for those few patients whose skin disease fails to resolve following drug withdrawal. Pemphigus and rheumatoid arthritis have both been associated with HLA DR4, which was present in all three of our patients who were tested. ***Key words: Autoimmune disease; HLA type.***

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The annual incidence of pemphigus is estimated to be 0.1–0.5 per 100 000 population (1). We present our experience of the high incidence of pemphigus foliaceous in the setting of a clinic studying cutaneous reactions to drugs used to treat rheumatoid arthritis.

PATIENTS AND CASE REPORTS

All patients seen in a rheumatology clinic over a period of 18 months who developed a suspected cutaneous reaction to antirheumatic drugs were reviewed in a dermatology clinic. Where possible a specific dermatological diagnosis was made and in all patients, where consent was given, a skin biopsy for histology and immunofluorescence was obtained.

Over a period of 18 months, 92 patients were seen from a population of 695 patients who were attending clinics for monitoring of their second line therapy.

All four patients reported had classical and definite rheumatoid arthritis as defined by the American Rheumatism Association criteria.

Case 1

A 62-year-old man with rheumatoid arthritis for 31 years presented with a 2-week history of a rash on his upper chest and back (Fig. 1) which he described as blisters which then scabbed over. He had been entered 4 weeks before into a double-blind placebo-controlled trial of a new anti-rheumatic drug and when the code was broken he was found to be on placebo. His only other medication was diclofenac 50 mg prn. He had not previously been treated with penicillamine but had earlier discontinued treatemnt with sodium aurothiomalate bacause of the development of a rash. There was no history of other autoimmune disorders. Clinically he had 5–1 cm diameter crusted lesions on his upper chest. Histology was non specific showing an epidermal erosion but immunofluorescence of perilesional skin showed deposition of IgG and C3 in the upper epidermis. Indirect immunofluorescence was negative. Other investigations included erythrocyte sedimentation rate (ESR) 74 mm/h, C-reactive protein (CRP) 14 mg/l (normal range 0–9 mg/l), rheumatoid factor (RhF) 1:640) and antinuclear antibody (ANA) 1:320. He was treated with auranofin 3 mg bd with resolution of the pemphigus foliaceus over 3 months.

Case 2

A 62-year-old woman with rheumatoid arthritis for 4 years presented with a 6 month history of red patches on her shoulders which then blistered. Her medication consisted of parenteral sodium aurothiomalate 50 mg fortnightly, which she had been on for the previous year, and indomethacin SR 75 mg daily. She had not been treated with other second line therapy. Her medical history included hypothyroidism for which she was taking thyroxine 50 μg daily. On examination she had 3 1 cm diameter erythematous patches between her shoulders. Histology revealed subcorneal blister formation with acantholysis (Fig. 2). Direct immunofluorescence showed deposition of IgG between keratinocytes and indirect immunofluorescence was negative. Other investigations included ESR 66 mm/h, CRP 20 mg/1, RhF 1:640 and ANA 1:640. HLA type A10(25), A19(29), B5(51), B12(44) and DR4. She was treated with topical betamethasone valerate and continued on the same dose of gold with improvement in her pemphigus.

Case 3

A 61-year-old man with rheumatoid arthritis for 15 years presented with a 4-month history of a scaly red rash on his face, scalp and central chest. He had noted that the extent of the rash varied with the dose of penicillamine, currently 250 mg daily, which he had been on for 2 years. He had been on doses of penicillamine up to 625 mg in the past. His other medication was indomethacin 75 mg bd. There was no history of other autoimmune disorders. Clinically he had extensive erythema and scale with some erosions on the face and scalp with well demarcated lesions on the central chest. Histology was nonspecific with epidermal erosions. Direct immunofluorescence was positive with intercellular staining of the epidermis with IgG. Indirect immunofluorescence was negative. Other investigations included ESR 7 mm/h, CRP 36 mg/1, RhF 1:160 and ANA 1:80. HLA type A2, A9(24), B12(44), B15, DR4. He was treated with topical clobetasol butyrate and withdrawal of the penicillamine with gradual improvement over 4 months. No other second line therapy was given for his arthritis.

Case 4

A 44-year-old woman with rheumatoid arthritis for 25 years presented with an asymptomatic scaling eruption of her chest for 5 weeks. Her medication included penicillamine 500 mg daily which she had been

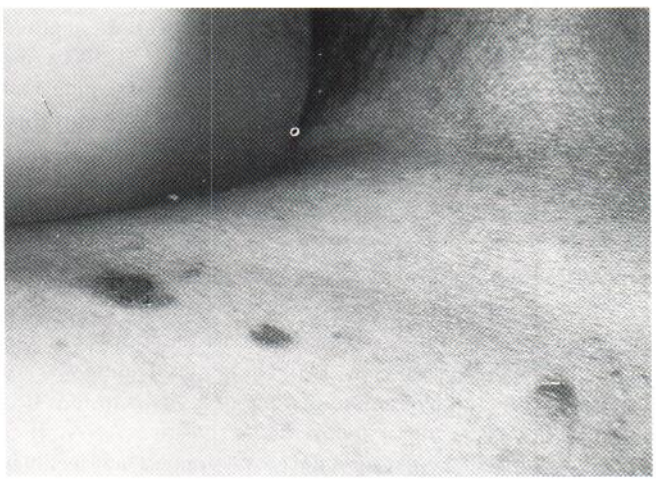

Fig. 1. Localised lesions of pemphigus foliaceous with erythema and scale on the upper back.

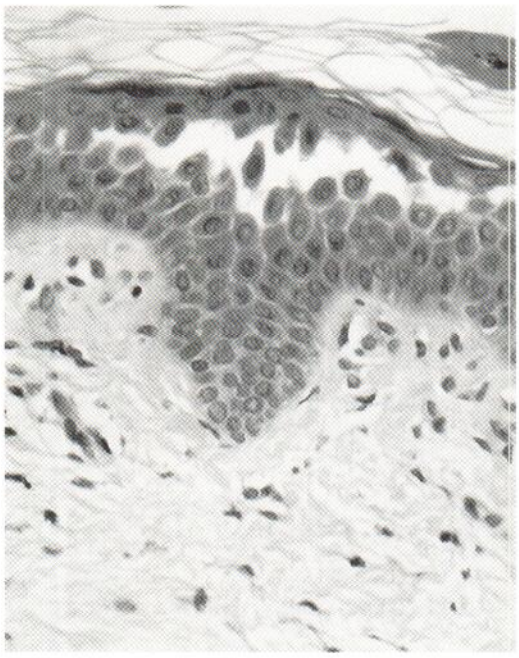

Fig. 2. Superficial epidermal split with acantholysis (H & E x200).

taking at that dose for 6 months and in total for 9 months. In addition, she had been taking sulphasalazine 500 mg daily for 8 years together with indomethacin 75 mg daily. Previous therapy for her arthritis included sodium aurothiomalate for 19 years. Clinical examination revealed discrete erythematous macules with a central erosion and peripheral scale. Histology revealed a superficial perivascular infiltrate with basal layer degeneration and the formation of colloid bodies. Direct immunofluorescence showed the deposition IgG, C3 and C4 between keratinocytes with the linear deposition of IgM along the basement membrane and within colloid bodies. Indirect immunofluorescence was negative. Other investigations included ESR 37, CRP 21, RhF 1:640 and ANA 1:320. HLA type A2, A19(31), B5, B16(39), DR4, DR8. Withdrawal of the penicillamine together with the use of topical fluocinolone acetonide resulted in resolution of the rash over 3 months.

DISCUSSION

Excluding the patients on penicillamine, the annual incidence of pemphigus foliaceous in this prospective group of rheumatoid arthritis patients is 1.9 per 1000 patients with rheumatoid arthritis requiring second line therapy. This is ~ 1000x the incidence in the normal population, strongly suggesting that this is a real association. We propose that rheumatoid arthritis be included with myasthenia gravis and thymoma (2–4) as a condition associated with pemphicus. The first two cases had mild disease and would not have independently sought a dermatological opinion and we suspect that this is the reason for this association not previously being recognised.

Direct immunofluorescence of normal skin in patients with rheumatoid arthritis may show perivascular deposits of immunoglobulin and complement (5) but epidermal staining was not reported in the relatively small sample of patients tested. It is notable that all of our patients had a positive ANA. It is recognised (6) that in drug-induced pemphigus intercellular antibodies circulate at a low titre and that other autoantibodies, including antinuclear, are a frequent finding. Whilst circulating intercellular antibodies may be found in other conditions, such as burns, the presence of positive direct immunofluorescence is thought to be specific to a diagnosis of pemphigus (1). The occurrence of rheumatoid arthritis with both bullous pemphigoid (7) and linear IgA disease (8) has been reported.

Pemphigus has been reported in association with HLA A10 in Japanese patients (9) as well as with HLA DR4 (10, 11) in Jewish patients. Rheumatoid arthritis is also associated with HLA DR4 (12) and this HLA association might explain the tendency of both diseases to occur in the same patient. In the three patients who agreed to testing all had HLA DR4 and two were homozygous for this allele. One patient had HLA A10 (25).

It is interesting that the patients on penicillamine had clinically more extensive disease despite negative indirect immunofluorescence which is usually used as a marker of disease activity (13). The original description of penicillamine induced pemphigus occurred in a patient with Wilson's disease (14) with positive immunofluorescence findings. However, whilst penicillamine can produce autoimmune disease it is also known to induce acantholysis in skin explants (15) and could therefore exacerbate pemphigus in patients with rheumatoid arthritis with mild or subclinical disease. This may also explain those reports of a bullous dermatosis with penicillamine with negative immunofluorescence findings (16, 17) and those reports of penicillamine induced pemphigus which fail to completely resolve following discontinuation of therapy (18).

The last patient had some features of cutaneous lupus erythematosus on routine histology. The immunofluorescence findings, however, combining features of both pemphigus and lupus erythematosus, were diagnostic of pemphigus erythematosus which has been reported following penicillamine therapy (19, 20).

In conclusion, we suggest that there is an association between rheumatoid arthritis and pemphigus foliaceous and that therapy with penicillamine, as well as causing pemphigus de novo, may exacerbate pre-existing disease.

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Familial Occurrence of Fixed Drug Eruptions

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Fixed drug eruptions following the use of pyrazolone derivatives occurred in 4 members of the same family: a 12-year-old girl, her grandmother, and two of her great aunts. Although the pathophysiologic events leading to this type of reaction are unknown, these cases of familial occurrence suggest that genetic predisposition might be an important causal factor. ***Key words: HLA; Pyrazolone derivatives.***

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Fixed drug eruptions (FDE) are considered to be the most classic form of cutaneous reactions to drugs. Clinical manifestations include the appearance of one or several round or oval erythematous lesions with clearly defined borders. The lesions are dusky red in colour. In some cases a central blister forms. After the acute phase of the reaction has subsided, the affected areas usually show hyperpigmentation that varies in shade from brown to brownish purple or even black (1). These lesions reappear in the same sites each time the offending drug is used. They may occur in any area of the body and involve either skin or mucous membranes. The number of reaction sites may gradually increase if the patient continues to use the drug from time to time (2).

The drugs that have most frequently been implicated in fixed drug eruptions include phenazones, barbiturates, sulfonamides, phenolphthalein, salicylates, tetracyclines and penicillin (3–6).

The pathogenesis of fixed drug eruptions remains uncertain. It is believed that the immune system plays a major role in these reactions (1), but there is also data to suggest that immunological mechanisms may not be the only causative factor (6). The present study describes 4 members of a single family who experienced FDE following administration of pyrazolone derivatives. Our findings in these cases suggest that there may be a genetic basis for this form of drug reaction.

CASE REPORTS

Case 1

A 12-year-old girl (Fig. 1) was seen in our outpatient clinic for stomatitis that had appeared three days before. Approximately 10 h prior to the appearance of the first symptoms, the child had taken 100 mg of feprazone (Zepelin, Istituto De Angeli) for treatment of cold symptoms.

Physical examination showed both lips to be edematous and covered with hemorrhagic scabs. There were several areas of edema with surrounding patches of erosion within the oral cavity itself. The clinical features of these lesions were compatible with a diagnosis of FDE. The symptoms resolved in about eight days with topical therapy.

The child had a history of atopy. She and her family clearly remembered three previous episodes of bullous stomatitis, all of which had occurred following the use of feprazone.

Case 2

The maternal grandmother of the child described above was seen in our clinic. The woman, 59 years old, presented a cutaneous rash and complained of dysphagia. She reported that three days prior to our observation, she had also taken 100 mg of feprazone. Five minutes later she experienced an intense burning sensation in the genital area and generalized pruritus. During the following 24 h, the patient noted the appearance of purplish erythematous lesions on her wrists, thighs, face and neck, areas of erosion in the vulva and erythema of the oral cavity with slight dysphagia.

Physical examination revealed the presence of four round lilac-coloured lesions approximatley 4 cm in diameter. The lesions were situated symmetrically, one on each forearm and one on each thigh. There were two other erythematous lesions, one on her right cheek and the other on the back of her neck. At the centers of some of these lesions there were blisters which continued to evolve, becoming more evident during the days that followed. Within the oral cavity and on the medial surface of the labia majora there were other areas of erosion with erythematous bases. She was admitted to the hospital.

The patient was afebrile and routine blood chemistry test results were within normal limits. She was started on antihistamines and topical steroids.

On the fifth day of hospitalization, a skin biopsy was performed at the margin of a blister on the patient's forearm. Histological examination of the hematoxylin-eosin stained sections showed separation of the epidermis from the dermis secondary to blister formation and epidermal necrosis. Further away from the blister, edematous degeneration of the basal and superbasal keratinocytes could be seen with isolated areas of necrosis. There was a slight lympho-histiocyte reaction in the perivascular dermis with incontinentia pigmenti. By the 15th day of hospitalization, the bullous lesions had for the most part resolved, leaving behind areas of light brown pigmentation.

This patient also reported the previous occurrence of a similar episode which was also related to feprazone use.

Cases 3 and 4

Following the hospitalization of Case 2, the patient's two sisters both reported that they too had experienced reactions to drugs in the past. The first sister (Case 3, Fig. 1), 48 years old, described three episodes, the most recent of which had occurred three years earlier. These reactions took place following the consumption of a capsule containing feprazone (Zepelin). Thirty minutes after taking the drug, the sister was stricken with generalized pruritus and facial erythema. A few hours later, hemorrhagic vesicles appeared on her lips, making it impossible to eat. During the next hours, round, purple lesions appeared on both her wrists. These latter lesions evolved into blisters. At the time of our interview with this woman, i.e. three years after the third and final episode, hyperpigmented areas were still apparent on her cheeks and wrists.

The second sister (Case 4, Fig. 1), 52 years old, reported three episodes of bullous stomatitis with a dark purple, intensely pruritic lesion on the elft wrist. All three episodes had their onsets approxi-

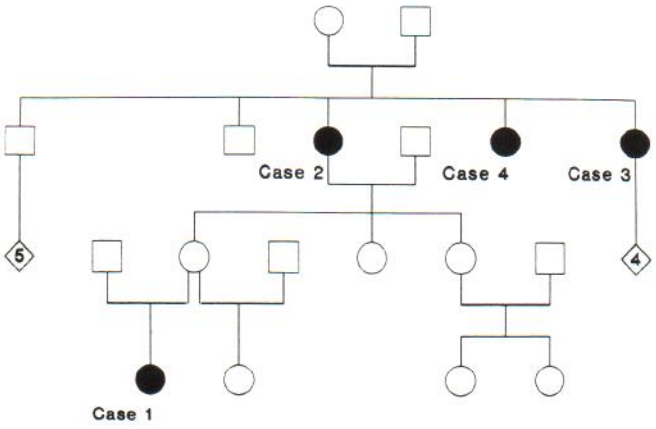

Fig. 1. Family pedigree.

mately 6–8 h after the woman had taken a drug containing propyphenazone and butalbital (Optalidon, Sandoz).

Laboratory findings

IgE levels were determined in all four subjects. Patients 2, 3 and 4 had levels of less than 15 IU/ml. Patient 1 had 180 IU/ml.

HLA typing was in patient 1: A1, A3, Bw55(w22), B35, Cw3, Cw4, Drw11(5), DRw6, DQw1, DQw3; in patient 2: A1, A2, Bw55(w22), B12, Cw3, DR4, DRw13(w6), DQw1, DQw3; in patient 3: A1, A2, Bw55(w22), B12, Cw3, DR4, DRw13(w6), DQw1, DQw3; in patient 4: A2, A28, Bw55(w22), B35, Cw3, DR4, DQw3.

Skin testing

All four patients were subjected to occlusive patch testing with feprazone (10% in white petrolatum) using the Finn chamber technique. Case 4 was also tested with propyphenazone (10% in white petrolatum). In Cases 1 and 2, the patch tests were performed six months after the cutaneous eruption had resolved. The patches were applied to normal skin on the back in Cases 1 and 4. In Cases 2 and 3, the patches were applied to areas previously involved in the cutaneous reactions. The patches were left in place for 24 h. Only Cases 2 and 3 presented positive reactions with local provocation of FDE, while patch tests performed on normal skin in cases 1 and 4 were, as expected (7), negative.

COMMENTS

Familial occurrence of fixed drug eruptions would seem to be fairly rare. In spite of the fact that these reactions are quite common, reports of even large series of patients either fail to consider familiarity or describe non-contributory family histories (2).

Fixed drug eruptions are one of the most common forms of adverse reactions to the pyrazolone derivatives (5).

Possible involvement of the HLA system had already been suggested for other types of drug reactions (8).

The HLA antigen B12 has, in fact, been found with increased frequency in patients with Stevens–Johnson syndrome with ocular complications as well as in those with Toxic epidermal necrolysis (9, 10). At this point, it is also interesting to note that the two cases with the more severe symptomatology reported here, Cases 2 and 3, were both positive for the HLA B12.

To our knowledge, there is no other data in the literature on HLA typing in patients with fixed drug reactions.

Although the pathophysiological events that lead to fixed drug eruptions remain unknown, our observation of this reaction in four members of the same family raises the possibility of genetic predisposition to this condition. Further study on a larger series of patients will be needed to determine whether there is indeed a consistent association between one or more HLA antigens and fixed drug eruptions.

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Acute Mercury Intoxication with Lichenoid Drug Eruption Followed by Mercury Contact Allergy and Development of Antinuclear Antibodies

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A 31-year-old black man was examined for evaluation of a suspected occupational disease. Three years earlier he had been suffering from acute mercury intoxication during work in a mercury recycling factory. Skin symptoms then had been a lichenoid drug eruption, patchy alopecia and stomatitis, which had all disappeared rapidly after systemic glucocorticosteroid treatment. The examination revealed positive patch test reactions to metallic mercury and inorganic mercury compounds, an elevated titre of serum antinuclear antibodies and normal IgE levels. The induction of antinuclear antibodies by mercury has been shown in animal experiments. It can be hypothesized that this patient, who may have had an increased individual susceptibility, became allergic to mercury by the mercury intoxication.

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The increasing exposure to harmful environmental chemicals has been discussed as a possible cause of immunologic disturbances in the human organism (1).

In animal experiments mercuric chloride can induce immune-complex glomerulonephritis, increase in immunoglobulin production (especially IgE), increase in B cells and T helper cells and the production of antinuclear antibodies (2, 3, 4).

In man, so far, mercury allergy is the only known immunologic disturbance. Mercury allergy can be of the anaphylactic type (e.g. anaphylactic reaction to thiomersalate, an organic mercury compound (5) or of the delayed type hypersensitivity (contact dermatitis, lichenoid reactions in red tattoo areas or adjacent to amalgam fillings, or baboon-syndrome (6–14)).

In lichenoid reactions caused by mercury positive patch test reactions are only rarely found. It is supposed that lichenoid eruptions, like other symptoms of mercury intoxication, are highly dependent on an individual susceptibility (15, 16).

The patient reported is a man who had developed a lichenoid eruption during acute mercury intoxication and in whom later antinuclear antibodies and positive patch test reactions to mercury were found.

CASE REPORT

A 31-year-old black man was examined in our clinic for assessment of a possible occupational disease. Three years earlier he had worked in a mercury recycling factory, where security measures against mercury contamination had been extremely deficient.

After only three weeks' work he had developed symptoms of acute mercury intoxication like stomatitis, patchy alopecia, generalized pruritus and subsequently a lichenoid rash. In his urine mercury was found in a concentration of 380 µg/l (the tolerable limit of urinary mercury concentration is 200 µg/l). The hospital treatment had consisted of systemic glucocorticosteroids and dimercaprol to accelerate the excretion of mercury. Healing of skin symptoms occurred rapidly as well as normalization of total mercury excretion. The definite diagnosis, confirmed histologically, was "lichen planus, presumably caused by mercury intoxication".

Other eliciting factors of lichen planus or lichenoid drug eruption like psychological stress, certain drugs, contact with aminoglycoside containing creams or certain film developers were excluded (8, 9, 20). There was no history of a previous allergic reaction.

Shortly after the mercury intoxication the patient complained about a generalized itch sensation after sun exposure, which he had not experienced earlier.

Dermatologic examination

Healthy looking slim black man with reticulate macular hyperpigmentations on the upper chest and the upper back. No signs of alopecia. Oral cavity without pathologic findings: one amalgam filling with normal surrounding gingiva.

Serologic examination

Direct immunofluorescence repeatedly showed antinuclear antibodies with a homogeneous pattern on Hep2 cells and a titre of 1:640. No evidence of ENA-, Ro-, La- and anti-ds-DNA-antibodies. The following parameters were normal: ESR, red and white blood chemistry, serum IgE level (8 kU/l; normal <100 kU/l). Hepatitis serology showed immunity for hepatitis A, no immunity for hepatitis B: Syphilis serology was negative. Human leukocyte antigens were HLA-A28, -A29, -B49 and Bw4. HLA-DR testing was negative for HLA-DR2 and HLA-DR3 (Prof. Dr. E. Albert, Kinderpoliklinik, Ludwig-Maximilians-University Munich).

Patch test (Table I)

The patch test ws performed and evaluated according to the rules of the International Contact Dermatitis Research Group using standard test reagents (Hermal, Reinbek and Dr. Brinkmann, Mönchengladbach) which had been proven to be non-irritative in 20 healthy volunteers. There were positive reactions to mercuric chloride (= sublimate), ammoniated mercury and mercuric amidochloride.

No test reactions were found towards the organic mercury compounds thiomersal sodium timerfonate, phenylmercuric borate and phenylmercuric nitrate.

Prick test

No type-I-reaction to aero-allergens nor to thiomersal, no type-III-reaction to thiomersal.*

Photosensitivity testing

Minimal erythema dosis for UV-B was normal, i.e. no erythema even at 220 J/cm^2 (polychromatic light, testing on gluteal region).

* In the pricktest performed with standard aero and food allergens as well as with thiomersalate (1% and 10%) there were no immediate wheat and flare reactions nor any positive reactions after 48 and 72 hours.

Table I. *Results of patch test with inorganic and organic mercury compounds*

	48 h	72 h
Inorganic mercury compounds:		
Metallic mercury 0.5% pet.	–	+
Amalgam (as is)	–	–
Ammoniated mercury 1% pet.	+	+
Mercury bichloride (sublimate) 0.1% pet.	+	+
Mercuric amidochloride 1.0% pet.	+	+
Organic mercury compounds:		
Thiomersal 0.2% pet.	–	–
Sodium timerfonate 0.1% pet.	–	–
Phenylmercuric nitrate 0.005% pet.	–	–
Phenylmercuric borate 0.005% pet.	–	–
Other compounds of standard patch test series	–	–

The histologic examination of a positive patch test reaction showed pronounced signs of a type-IV-reaction such as parakeratosis, spongiosis and exocytosis of lymphocytes, dense perivascular lymphocytic infiltrate in the upper dermis intermingled with eosinophils and reaching partly down to the mid dermis.

Direct immunofluorescence of this sample: There were no deposits of immunoglobulins (IgG, IgM, IgA), complement, nor fibrinogen.

DISCUSSION

The case presented here demonstrates the occurrence of mercury contact allergy and antinuclear antibodies after acute mercury intoxication. It is assumed – although not proven – that these changes were not present before the occupational exposure.

The patient seemed to have a certain susceptibility to react with symptoms of mercury intoxication, while other workers in the factory did not show any symptoms despite of even higher exposure as measured by increased urinary mercury concentrations.

An individual susceptibility is regarded as important factor in developing lichen planus, the differential diagnosis versus lichenoid drug eruption. yet, lichen planus is usually a chronic disease, which may be associated with autoimmune diseases or may occur during graft-versus-host reaction and which often shows an association with the histocompatibility antigen HLA-A3 (7, 17, 18, 22, 23, 24, 25).

The diagnosis "lichenoid drug eruption" caused by mercury compounds is supported by the following criteria: rapid healing after mercury excretion, absence of HLA-A3 together with the positive patch test reactions to mercury and inorganic mercury compounds.

Lichenoid contact dermatitis has been described in patients with sensitization to aminoglycoside antibiotics and colour film developers (19, 20). Moreover, it is known that contact allergy to mercuric sulphide (cinnabar), the red tattoo colour, may induce lichenoid lesions or, rarely, lesions resembling discoid lupus erythematosus (7, 22, 26, 27, 28).

In animal experiments mercuric chloride has been shown to transiently induce immune-complex glomerulonephritis, development of nuclear antibodies, a marked increase in serum IgE as well as activation of B cells and T helper cells in some species. This induction is rather independent from a total body mercury dose but related to a genetic, strain-specific susceptibility (3, 4, 23).

In our patient, antinuclear antibodies showing a homogenous staining pattern in indirect immunofluorescence on Hep2-cells were present in a titre of 1:640. In animals treated with mercuric chloride antinuclear antibodies also showed the homogenous pattern and, differing from one patient, a nucleolar pattern (3). The nuclear antigen reacting with antinuclear antibodies of the homogenous type has not yet been identified; the antinucleolar antibodies found in mice treated with mercuric chloride treated are probably directed against the nucleolar antigen fibrillain (29). No explanation for the presence of antinuclear antibodies other than mercury intoxication was found in our patient, who was otherwise healthy. In particular, there were no clinical signs compatible with the diagnosis of a collagen-vascular disease, i.e. lupus erythematosus, systemic scleroderma or dermatomyositis. The family history was also negative (30, 31). Only the fact that the patient was suffering from generalized pruritus after sun exposure since the time of the mercury intoxication might – very speculatively – be seen in the context of an increased light sensitivity of an incipient otherwise silent lupus erythematosus. Therefore, a possible clinical relevance of the increased antinuclear antibodies in the future cannot be excluded. Follow-up studies will show whether the patient's symptoms are transient, as they were in animal experiments, and whether the antibody titres will decline. This would be a further indication that, also in man, mercury compounds could act as precipitating factors initiating an abnormal autoimmune response.

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Roxithromycin in Lyme Borreliosis: Discrepant Results of an *In vitro* and *In vivo* Animal Susceptibility Study and a Clinical Trial in Patients with Erythema Migrans*

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A new semisynthetic macrolide roxithromycin was evaluated for its potential use in the treatment of Lyme borreliosis. Using a macro-dilution broth technique, *Borrelia burgdorferi* was shown to be susceptible to roxithromycin with a minimal bactericidal concentration (MBC) of 0.06–0.25 μg/ml. A systemic *B. burgdorferi* infection was established in gerbils; a dosage of ≥ 25 mg/kg/day roxithromycin for 10 days eliminated the infection. A single blind, randomized multicenter study was performed to evaluate the efficacy of roxithromycin 150 mg b.i.d. versus phenoxymethyl-penicillin 1 g b.i.d. for 10 days in patients with uncomplicated erythema migrans. The study was interrupted when 19 patients had enrolled because of five treatment failures. All 5 patients had received roxithromycin; three patients had persisting or recurrent erythema migrans, one developed a secondary erythema migrans-like lesion and severe arthralgia and one developed neuroborreliosis. *B. burgdorferi* was isolated from skin biopsies after roxithromycin therapy from two patients with persistent erythema migrans and both isolates were still highly susceptible to roxithromycin (MBC = 0.03 μg/ml). No treatment failures were seen in 10 patients treated with phenoxymethyl-penicillin. Roxithromycin is thus not recommended for treatment of Lyme borrreliosis.

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Lyme borreliosis (LB) is a tick-borne multisystemic spirochetosis caused by *Borrelia burgdorferi*. It is now the most frequent vector-transmitted human infectious disease in Europe and USA. Penicillin and tetracycline were early shown to be effective (1, 2) and are currently the most widely used antimicrobial agents for Lyme borreliosis. Whereas *B. burgdorferi* is highly susceptible to erythromycin in vitro (3, 4), it is a common experience that treatment failures may occur when erythromycin is used in patients with Lyme borreliosis (1). The reason for this discrepancy is unknown. We speculated whether the low therapeutic efficiency of erythromycin might be due to insufficient dosage and low bio-availability after oral administration and whether a new semisynthetic macrolide roxithromycin could be more effective. Compared to erythromycin, roxithromycin has a significantly higher bio-availability, tissue penetration and potency (5). The question is relevant because we still lack an alternative oral therapy in children and pregnant women allergic to penicillin.

The aim of this study was first to investigate the in vitro and in vivo animal susceptibility of *B. Burgdorferi* to roxithromycin and, if favourable, to perform a comparative clinical trial of roxithromycin versus penicillin in patients with uncomplicated erythema migrans.

MATERIALS AND METHODS

In vitro study

We used 8 *B. burgdorferi* strains as listed in Table I; except DK6 which was isolated from the CSF of a patient with neuroborreliosis all other strains were isolated from skin biopsies from patients with erythema migrans (n = 2) and acrodermatitis chronica atrophicans (n = 5). The antimicrobial agents tested were: penicillin, erythromycin, roxithromycin, doxycycline and ceftriaxone. The antibiotic susceptibility of *B. burgdorferi* was studied by the macrodilution broth technique in BSK medium to determine minimal bactericidal concentrations (MBCs) – the lowest antimicrobial concentration to completely inhibit growth of *B. Burgdorferi*. The concentrations of the agents tested ranged from 0.03 μg/ml to 32 μg/ml. Duplicate tubes containing 7 ml BSK medium with antimicrobial agents and control tubes without antimicrobial agents were inoculated to a final density of 10^5 log phase *B. burgdorferi*. After 7 days of incubation at 32°C 0.1 ml of the medium was transferred to 7 ml BSK medium without antimicrobials and incubated for a further 7 days. The spirochete cell count of the last culture was then read by darkfield microscopy.

In vivo study

A systemic *B. burgdorferi* infection was established in gerbils (weight 70 g) by intraperitoneal inoculation of 10^8 low passage spirochetes, either strain DK1 or DK7. Before inoculation the spirochetes were washed once and resuspended in PBS. One week after inoculation roxithromycin was given twice daily for 10 days subcutaneously at 5 mg/kg/day (4 animals), 25 mg/kg/day (8 animals) and 125 mg/kg/day (6 animals). Twenty-five gerbils inoculated with *B. burgdorferi* at the same time did not receive antibiotic treatment and served as controls. One week after the last roxithromycin dose all animals were killed and a culture for *B. burgdorferi* in BSK medium was initiated from spleen, kidney and urinary bladder tissue. Triplicate culture tubes from every organ were incubated at 32°C and examined by darkfield microscopy weekly for 1 month as previously described (6). The in vivo susceptibility was expressed as the lowest roxithromycin dose which could eradicate the *B. burgdorferi* infection.

Clinical trial

We performed a, for the investigator, single blind, randomized multicenter study with parallel groups of patients receiving either roxithromycin 150 mg b.i.d. or phenoxymethyl-penicillin 1 g b.i.d. for 10 days. Because of the high rate of spontaneous cure of erythema migrans it was estimated that 100 patients were necessary, 50 patients in each treatment group, for a significant difference to be detectable. Patients were recruited from five Danish and three Swedish dermatological

*The results of this study were presented at the 4th International Conference on Lyme Borreliosis, Stockholm 18.–21. June 1990.

Table I. *MBC (μg/ml) of 5 antimicrobials against 8 strains of B. burgdorferi*

Borrelia burgdorferi strains	Penicillin	Roxithromycin	Erythromycin	Ceftriaxone	Doxycycline
DK1	4.0	0.12	0.03	0.03	0.50
DK2	2.0	0.12	0.50	0.03	2.0
DK3	0.5	0.12	0.12	0.03	0.50
DK4	0.5	0.06	0.06	0.03	2.0
DK5	0.5	0.12	0.06	0.06	0.50
DK6	4.0	0.25	n.e.	n.e.	n.e.
DK7	1.0	0.25	n.e.	n.e.	n.e.
S ACA 1	4.0	0.25	0.25	0.06	4.0
MBC range	0.50–4.0	0.06–0.25	0.03–0.50	0.03–0.06	0.50–4.0
median	2.0	0.12	0.12	0.03	2.0

n.e. not examined

centers during the summer 1989. Only otherwise healthy patients > 17 years old and with a uncomplicated erythema migrans based on clinical evidence were included. At the pretreatment visit a physical routine laboratory and borrelia serological examination of the patients were performed. In two patients with pronounced constitutional symptoms the cerebrospinal fluid was examined and normal findings excluded neuroborreliosis. During and after treatment the patients were requested to record the course of the erythema, general symptoms and side effects on a special report form. Patients were followed up 3–6 weeks and 6 months after therapy. In some patients skin biopsies were taken for histopathology and spirochetal cultivation. The evaluation of drug efficacy was based on the clinical outcome. The study was approved by the Danish (ref. no. 1989-1-53) and Swedish ethics committees (ref. no. 88-59).

RESULTS

The results of the in vivo susceptibility study are summarized in Table I. All *B. burgdorferi* strains were susceptible to roxithromycin in vitro with an MBC of 0.06–0.25 μg/ml. Comparable values were obtained for erythromycin. MBCs for penicillin were considerably higher and revealed a pronounced variation between strains 0.5–4.0 μg/ml. Ceftriaxone showed the lowest MBC.

The results of the in vivo animal susceptibility study are shown in Table II. In 20 of 25 untreated infected gerbils a systemic *B. burgdorferi* infection could be demonstrated by a positive organ culture. Roxithromycin, 5 mg/kg was ineffective, whereas all organ cultures were negative in 14 animals receiving ≥ 25 mg/kg/day roxithromycin for 10 days.

The clinical trial was interrupted within three months and blindness was broken because of five treatment failures among the 19 patients who had by that time entered the study. These 19 patients consisted of 9 males, 10 females with a median age of 54 years (26–71 years); the median duration of their erythema migrans at the time of diagnosis and treatment start was 8 days (1–60 days). Serological examination for anti-*B. burgdorferi* antibodies revealed that before therapy one patient was IgG seropositive and 2 patients were IgM seropositive; a seroconversion 3–6 weeks after therapy was found in two patients regarding IgG and in 5 patients regarding IgM antibodies to *B. burgdorferi*. All 5 treatment failures occurred among the nine patients who had received roxithromycin. The treatment failures occurred at four different participating centers. The 5 patients did not differ in age, disease duration or severity from the remaining patients. Three patients showed persistent or recurrent erythema migrans. In 2 of them *B. burgdorferi* was isolated from a skin biopsy after roxithromycin therapy. One patient with an erythema migrans on the left leg developed a secondary erythema migrans-like lesion one week after start of roxithromycin treatment. The skin lesions disappeared a few days after the treatment was completed. However, 2 weeks later the patient complained of severe arthralgia in the left hip and knee but no joint swelling was found. The fifth patient developed a severe back pain 7 days after the last roxithromycin dose. On admission to hospital a lumbar puncture revealed lymphocytic pleocytosis (190 cells/μl) but no borrelia specific antibody synthesis in CSF. The findings were consistent with early neuroborreliosis and the patient recovered completely on a 10-day-course of high dose intravenous penicillin G.

Table II. *In vivo animal study of B. burgdorferi susceptibility to roxithromycin*

Roxithromycin dose (mg/kg/day)	*B. burgdorferi* strain used for infection	Number of gerbils		
		Infected	Culture positive	
0	DK1	9	5/9	20/25
0	DK7	16	15/16	
5	DK1	4	4/4	
25	DK1	3	0/3	0/8
25	DK7	5	0/5	
125	DK1	3	0/3	0/6
125	DK7	3	0/3	

After the blindness of the study was broken all patients treated with roxithromycin were, regardless of persisting symptoms, retreated with phenoxymethyl-penicillin. During the follow-up period of 5 to 10 months none of the 19 patients developed further symptoms or serological evidence of persistent infection.

We tested the in vitro susceptibility to roxithromycin of the two *B. burgdorferi* strains which were isolated from two recurrent erythema migrans lesions after roxithromycin therapy. Both isolates were still fully susceptible (MBC 0.03 μg/ml). Shortly before starting the blinded clinical trial a female with erythema migrans was treated with roxithromycin 150 mg

b.i.d. for 10 days at one of the participating centers. The erythema migrans faded but recurred shortly afterwards. *B. burgdorferi* was isolated from a skin biopsy in this patient before and after roxithromycin therapy. Both isolates were equally susceptible to roxithromycin (MBC 0.06 μg/ml; 0.12 μg/ml).

DISCUSSION

The therapeutic failure of roxithromycin 150 mg b.i.d. for 10 days in patients with erythema migrans was unexpected, considering the high in vitro susceptibility and its efficacy in the in vivo animal model. The in vitro susceptibility of *B. burgdorferi* to roxithromycin was comparable with previous reports (7). However, regarding the susceptibility in the animal model results were discrepant compared with a recent study (7), where roxithromycin was not effective in the gerbil. However, an important difference in the design of the two studies could explain the different results. In the other study, roxithromycin was given as a single daily dose for 7 days, while we administered the drug twice a day for 10 days. Considering the significantly higher drug clearance in small laboratory animals compared to humans (8), an antimicrobial agent should always be administered in divided doses and for at least 10 days, comparable to the therapy recommendations for human Lyme borreliosis (9). Equally inappropriate administration of i.e. penicillin to *B. burgdorferi* infected gerbils (4) and hamsters (3) is very likely the explanation for the often cited inefficacy of penicillin to eradicate *B. burgdorferi*. In both studies penicillin was given only once a day and only for 7 and 5 days respectively. In a previous study we found that penicillin given 3 times a day for 10 days eradicated a systemic *B. burgdorferi* infection in gerbils (10). Considering agents with very long half-lifes, i.e. ceftriaxone, the administration only once a day may not interfere with their high efficacy in the animal model (3, 4).

Similarly, results from in vitro susceptibility studies of *B. burgdorferi* do not always allow one to predict the clinical efficacy of the drug. Roxithromycin was despite of low MBCs not effective. On the other hand, penicillin has shown rather high MBC values (3, 4). Because of this the role of penicillin in the therapy of Lyme borreliosis (11, 12) has been questioned, although firmly verified treatment failures in documented cases of Lyme borreliosis treated appropriately with penicillin are very rare. An explanation for the low in vitro susceptibility of *B. burgdorferi* to penicillin may very likely be the instability of the compound (13) when it is incubated in the culture medium at 32–35°C for 8 days (4) or even 6 weeks (3).

The efficacy of penicillin obtained in the present clinical trial is in accordance with previous experiences of patients with erythema migrans (2) and patients with neuroborreliosis (14, 15). The mechanism for therapeutic failures of the two macrolides erythromycin and roxithromycin is obscure. MBCs of three strains obtained after roxithromycin therapy did not show any development of resistance. In analogy high rates of treatment failure have been reported in patients with primary and secondary syphilis treated with erythromycin (16) despite of a high in vitro activity. Erythromycin is thus no longer listed as a recommended equally effective alternative to penicillin or tetracyclin for the treatment of syphilis (17). Roxithromycin has shown a highly species-dependent protein binding ranging from 7% in rabbits, 30% in rats to 86% in humans (18). This fact may influence: (I) the in vitro determined MBCs because BSK medium contains rabbit serum and bovine serum albumin and (II) the different results obtained from infected humans and laboratory animals treated with roxithromycin. Another new semisynthetic macrolide azithromycin has recently been shown to be highly effective against *B. burgdorferi* in vitro and in infected gerbils and hamsters (7, 19). A clinical evaluation of this compound in Lyme borreliosis would be of great interest.

Recently two patients presumed to have Lyme borreliosis were reported to improve on combined treatment with roxithromycin and cotrimoxazole (trimethoprim/sulphamethoxazole) (20, 21). Both patients had been refractory to penicillin and one even to ceftriaxone therapy. These reports do not agree with the lack of roxithromycin efficacy in Lyme borreliosis demonstrated in this paper. Moreover it is surprising that co-trimoxazole, which is used to avoid contamination in *B. burgdorferi* cultures (22), was reported to be effective. Such cases should, like other presumed penicillin treatment failures that have been reported, lead to a critical reevaluation of the diagnosis. The outcome of this clinical trial furthermore confirmed previous estimates (2) of the incidence of neuroborreliosis (12%) in European patients with untreated erythema migrans.

We conclude that roxithromycin 150 mg b.i.d. is not a recommendable treatment in Lyme borreliosis and that antimicrobial susceptibility studies of *B. burgdorferi* in vitro and in animal models should be interpreted with caution.

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Subcorneal Pustular Dermatosis in a Patient with Crohn's Disease

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A case of subcorneal pustular dermatosis (Sneddon–Wilkinson disease) is reported in a patient with a one-year history of Crohn's disease. Subcorneal pustular dermatosis has been described in association with monoclonal gammopathy, but to our knowledge it has not been associated with Crohn's disease. This new association reinforces the hypothesis of a possible common pathogenesis for neutrophilic dermatoses and inflammatory bowel diseases. ***Key words: Neutrophilic dermatoses; Ulcerative colitis; Pyoderma gangrenosum; Sweet's syndrome.***

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Subcorneal pustular dermatosis (SPD), also referred to as Sneddon–Wilkinson disease, is a chronic relapsing vesiculopustular eruption, mainly involving the trunk and intertriginous areas, usually seen in women past the age of forty (1). Its association with a monoclonal gammopathy, most commonly an immunoglobulin A-paraproteinemia, is well recognized (2). SPD has also been occasionally described in patients with rheumatoid arthritis (3) and ulcerative colitis (4), but the association with Crohn's disease has not previously been reported.

CASE REPORT

A 37-year-old man was admitted to our department with a one-month history of a pustular eruption. One year before admittance, a diagnosis of ileocolonic Crohn's disease had been made on the usual clinical, morphological and histological criteria (5). A first cousin of him was also known to suffer from Crohn's disease. At his admission, Crohn's disease was well controlled, i.e. Crohn's disease activity index < 150 (6), by mesalazine (1.5 g per day).

On physical examination, he presented with flaccid pustules with hypopyon on erythematous bases involving the trunk, axillae, groin folds and arms. Recurrent waves of lesions coalescing led to circinate and polycyclic patterns. There was no fever or diarrhea. Histology of a pustular lesion showed a subcorneal pustule filled with polymorphonuclear leucocytes, mainly neutrophils (Fig. 1). A perivascular dermal infiltrate was present, consisting predominantly of neutrophils and rarely eosinophils. There was no spongiosis or acantholysis. Direct and indirect immunofluorescence were negative. Haematological investigations and a full biochemical screen were normal and no paraprotein was detected.

A diagnosis of SPD was made on the basis of the clinical picture together with the histopathological findings. The patient was given dapsone 100 mg daily which led to control of cutaneous lesions within 6 weeks. At a follow-up six months later, the skin lesions had not recurred.

DISCUSSION

Crohn's disease may have distinctive mucocutaneous manifestations which may be related to the primary granulomatous process, to nutritional deficiencies, to therapy or may be idiopathic in nature. Idiopathic conditions include erythema nodosum, epidermolysis bullosa acquisita, necrotizing vasculitis, finger clubbing and neutrophilic dermatoses (7).

Neutrophilic dermatoses, e.g. SPD, intra-epidermal neutrophilic immunoglobulin A dermatosis, Sweet's syndrome, pyoderma gangrenosum and erythema elevatum diutinum, are non-infective skin diseases without any known etiology, characterized by a cutaneous neutrophilic infiltrate (8). Reports of overlap syndromes between those conditions (9, 10), together with the efficacy of drugs acting on neutrophils, have led to the concept of the neutrophilic dermatoses clinicopathological spectrum. Furthermore, these dermatoses share possible association with a similar range of diseases including myeloproliferative disorders (11) and evolutive inflammatory bowel diseases, i.e. Crohn's disease and ulcerative colitis. Pyoderma gangrenosum is by far the most frequent neutrophilic dermatosis occurring in inflammatory bowel diseases, especially ulcerative colitis (9). Sweet's syndrome has been reported in association with Crohn's disease in four patients (12, 13, 14) and erythema elevatum diutinum has been mentioned in one case (15). Up to now, SPD has only been recorded in one patient with a non-evolutive ulcerative colitis (4). Interestingly, in our case, the bowel disease was also quiescent. Although concurrence of SPD and Crohn's disease may be coincidental, the probability of two rare conditions occurring together seems low. This observation enlarges the spectrum of neutrophilic dermatoses associated with inflammatory bowel diseases and raises the question of a possible common pathogenesis for these two groups of diseases. Neutrophils could be the causal link.

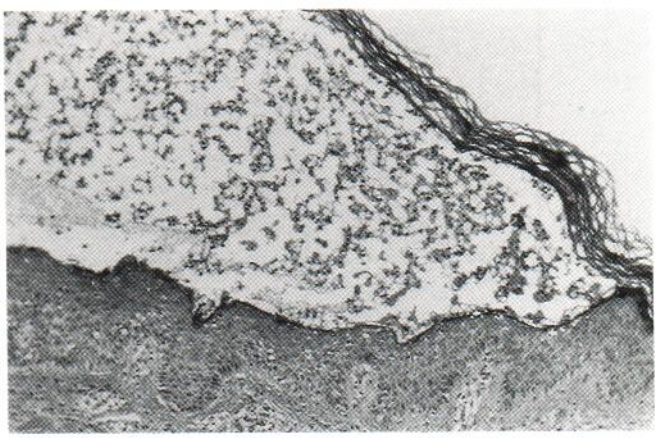

Fig. 1. Subcorneal pustule containing numerous neutrophils (H&E; ×100).

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Digital Verrucous Fibroangioma: A New Variant of Verrucous Hemangioma

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In this article, we report on 4 cases of a dome-shaped nodule on the dorsum of the finger, which had been present since birth and slowly enlarged. On light microscopic examination, these nodules showed similarities to verrucous hemangioma. However, they werre characterized by distinct clinical features and proliferation of dermal connective tissue. We consider these tumors to be a variant of verrucous hemangioma and propose to term them digital verrucous fibroangioma.

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We have encountered 4 characteristic cases of a benign neoplasm which revealed a benign, brownish, slightly rough surfaced nodule on the dorsum of the finger, present since birth. They histopathologically resemble verrucous hemangioma. However, they do not only have clinically characteristic features but also show proliferaiton of dermal connective tissue. We cannot find any report of a similar case and refer to our cases by the term "digital verrucous fibroangioma".

CASE REPORTS

Case 1

A 3-year-old Japanese boy noticed an asymptomatic, dome-shaped, skin-coloured nodule on the central dorsum of the left fourth finger, which had been present since birth. The nodule slowly enlarged and changed to brown during its growth. The boy visited us to have it removed. The nodule was soft, purplish brown, spherical in shape with a diameter of 12 mm, and located on the dorsum of the middle phalanx of the fourth finger of his left hand (Fig. 1). The surface of the nodule was slightly rough and scattered with black dots. It was movable from the underlying tissue. The lesion was surgically excised. No recurrence was seen. Histological examination revealed moderate hyperkeratosis and acanthosis. Some capillaries in the papillary dermis were markedly dilated (Fig. 2). The dermis, especially the middle and the lower dermis to the subcutaneous tissue, showed numerous dilated blood vessels, which were of varying size and filled with blood. Most of the blood vessels were composed of a single layer of endothelial cells. A proliferation of immature endothelial cells was scattered. Moreover, the dermis showed abundant collagen fibers (Fig. 2), and numerous cells with phagocytized brown granules were distributed around the sweat glands and between the collagen fibers. Numerous positive cells with iron staining were seen in the dermis.

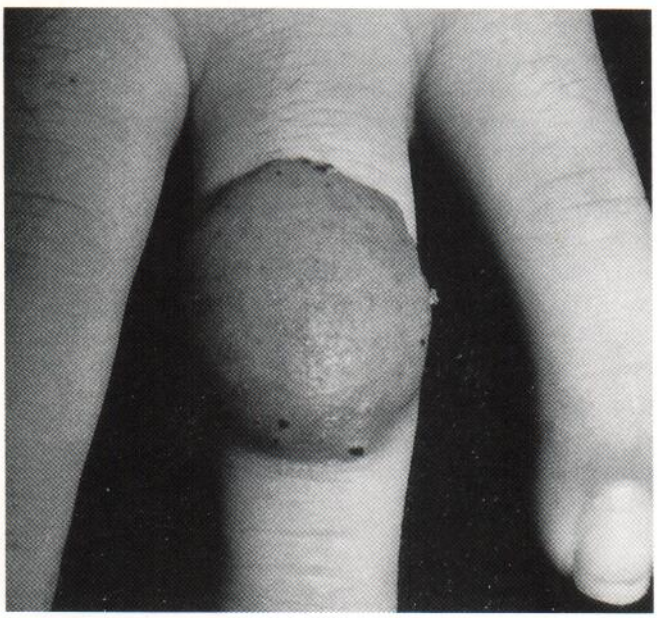

Fig. 1. Case 1.

Case 2

A 10-year-old Japanese boy was referred to our department. A small nodule had been present on the dorsum of his left third finger since birth. The nodule slowly enlarged as the child grew up. Physical examination revealed a firm, brownish, dome-shaped lesion on the

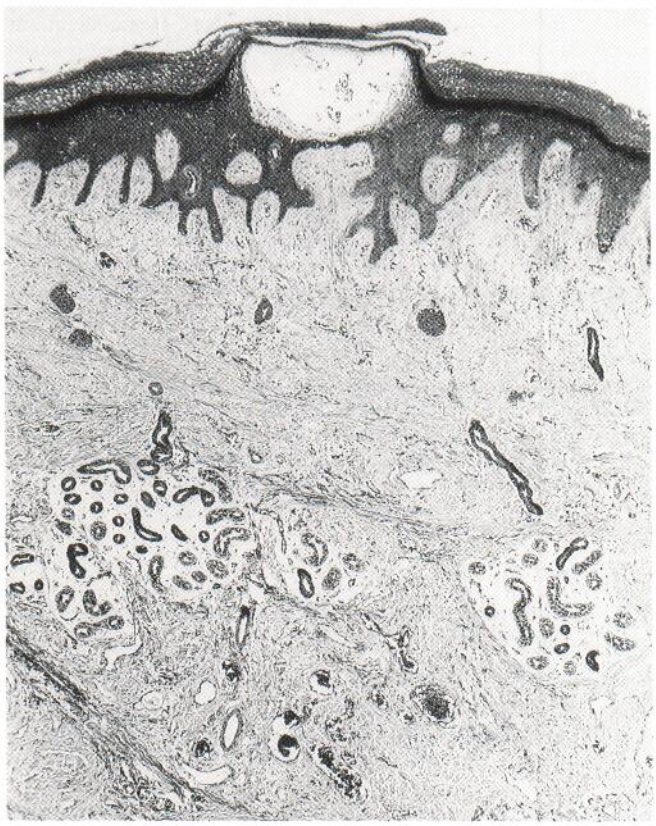

Fig. 2. Markedly dilated capillary is present in the papillary dermis. There are numerous dilated blood vessels filled with blood in the entire dermis associated with abundant collagen fibers. (hematoxylin eosin stain; original magnification, ×30).

Table I. *The clinicopathological details of our cases*

Patient No.	Age year/sex	Site	Onset	Appearance	Histological changes		
					Epidermis	Blood vessel	Connective tissue
1	3/M	lt. finger (IV) dorsum	at birth	Dome-shaped Black dot (++)	+	+	+
2	10/M	lt. finger (III) dorsum	at birth	Dome-shaped Black dot (one)	+	+	+
3	15/F	lt. finger (I) dorsum	at birth	Dome-shaped Black dot (++)			
4	2/F	lt. finger (III) dorsum	at birth	Dome-shaped Black dot (−)			

dorsum of the middle phalanx of the third finger of his left hand. The surface, with one black dot, was slightly rough. It was movable from the underlying tissue. It was surgically excised. At that time, the nodular lesion was well demarcated, and under the thickening dermis numerous dilated veins were coiled. Histologic examination revealed hyperkeratosis and elongation of the rete ridges. In the papillary dermis, the dilated capillaries were scattered. Numerous dilated blood vessels filled with blood were distributed in the deep dermis. These blood vessels were composed of a single layer of endothelial cells and partially demonstrated the capillary proliferations. Moreover, the thick collagen bundles were increased and numerous cells bearing hemosiderin were present between collagen fibers. Hemosiderin was confirmed by the special iron staining and seen between the collagen fibers and around the sweat glands.

Case 3

A 15-year-old Japanese female presented with an asymptomatic, firm nodule on the dorsum of the thumb of her left hand, present since birth. Earlier the lesion had slowly enlarged, but recently there had been no change in size. Physical examination revealed a 16×17×7-mm, brownish, spherical tumor, the surface of which had a small crowded area of black dots. The tumor was freely movable.

Case 4

A 4-year-old Japanese girl presented with an asymptomatic small nodule on the dorsum of the middle finger of her left hand, present since birth. The lesion had been enlarging gradually. It was a 11×11×7 mm, firm, well-defined, dome-shaped, brownish nodule. The surface was slightly rough. The mobility was good.

DISCUSSION

The 4 cases reported here demonstrate identical characteristic clinicopathological features (Table I): 1) The tumor presented at birch. 2) The lesions were restricted to the dorsum of the finger, 3) The tumor was firm or soft (elastic), purplish brown, well-defined, and dome-shaped, and 4) The surface was slightly rough and showed scattered black dots. On the other hand, the histopathological features did not only consist of epidermal changes but also fibrous stroma and vascular changes, which were composed of 5) dilated capillaries in the papillary dermis, 6) numerous dilated blood vessels filled with blood in the dermis through the subcutaneous tissue, 7) thick collagen bundles in the dermis, and 8) deposition of hemosiderin in the entire dermis.

The findings of the epidermis and the dermis to the subcutaneous tissue are compatible with angiokeratoma and cavernous hemangioma, respectively. Therefore, their histopathologic features seem to correspond to verrucous hemangioma (1) except for the dermal connective tissue change. However, our four cases differ from verrucous hemangioma in clinicopathological features. As to verrucous angioma, the verrucous appearance of the epidermis is considered to be caused by secondary reaction against underlying cavernous hemangioma. In our cases, the thick collagen bundles did not reveal any special arrangement such as a storiform pattern, and lacked proliferation of fibroblast. We speculate that a proliferation of dermal connective tissue seen histologically may be caused by reactive or secondary reaction based upon vascular change or a special anatomical site such as the dorsum of the finger rather than neoplastic change.

On the basis of the comparison made, we believe our cases to be a variant of verrucous hemangioma, a distinct clinical and pathological entity. We cannot find any report of a similar case. Therefore, we propose to refer to our cases by the term "digital verrucous fibroangioma".

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PUVA Treatment of Vitiligo: A Retrospective Study of 59 Patients

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We have performed a retrospective study of 59 patients with vitiligo who received PUVA therapy from 1972 to 1986. Sixteen patients had generalized vitiligo and 43 vitiligo in four locations (focal vitiligo). In both groups there were repigmentation in 44% of the patients. Half of the repigmented patients had improved more than 50%. None developed hypertrichosis, actinic keratosis, lentigines, or skin cancer within the observation period. Regardless of the results of PUVA therapy half of the patients thought PUVA was an acceptable therapy. ***Key words: Hypopigmentation; Psoralen; Vitiligo.***

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Parrish et al. reported in 1976 that psoralens in combination with high intensity ultraviolet light (PUVA) could stimulate repigmentation in persons with vitiligo (1). This therapy carries certain health risks and is time-consuming for both patients and doctors. We therefore thought it would be interesting to evaluate the efficacy of the treatment.

PATIENTS AND METHODS

Patients

The study is retrospective and includes 59 patients with vitiligo. Forty-one females and 18 males were treated with PUVA in the Department of Dermatology, Marselisborg Hospital, Denmark, during the period 1972 to 1986. The age range of the patients was 26 to 66 years. We extracted the following information from patients records: photographs, family history, sex, age at start of vitiligo, age at start of treatment, localization of vitiligo (face, hands, feet, trunk, arms, legs), number of treatments before start of repigmentation, and total number of irradiation. Vitiligo was graded in generalized vitiligo, which is defined as vitiligo in all localizations, and focal vitiligo, which is defined as vitiligo in less than six localizations (see above). The degree of pigmentation was graduated as 0%, 25%, 50%, 75%, or 100% by extracting data from the medical records and comparing photographs before and after treatment. These photographs were taken according to a standard schedule at each control visit, which took place once yearly for 5 consecutive years following cessation of PUVA therapy, in order to evaluate occurrence of skin cancer. This is according to Danish Health regulations.

Irradiation

UVA-irradiations were given in a UVA cabin with 39 Philips light tubes TL/40/09 (flux 9,0 mW/cm^2). One hour before exposure to UVA-light patients took psoralen. Treatment was given twice or three times weekly. Different psoralens were used during the observation period: methoxypsoralen, 8-methoxypsoralen, or 4,5,8-trimethylpsoralen. The treatment schedule was 1/2 joule/cm^2 at start, increasing at every third treatment with 1/2 joule/cm^2 up to 4 joule/cm^2, which was the maintenance dosage. The increments were prolonged if burning of the skin occurred. The various psoralens were given in recommended dosages.

Follow-up

At the time of evaluation we contacted 53 of the 59 patients who were treated with PUVA. Four patients had left the country and 2 were dead. The patients were contacted by telephone and asked for distribution of vitiligo at present compared with the distribution when treated. In addition we asked if sunbathing was now easily tolerated, or if the patients had observed skin tumors following their last 5-year control visit. Finally we asked if PUVA therapy had been an acceptable and worthwhile treatment.

RESULTS

Among the 59 patients 31% had a family history of vitiligo. Sixteen patients (27%) had generalized vitiligo and 43% focal vitiligo. Patients with focal vitiligo had symptoms in up to four different locations. None of the patients had vitiligo exclusively on the face, hands, or feet. The mean age at start of vitiligo was 21 years; the mean age at start of treatment was 30 years.

The mean cumulative UVA-dose was 338 joule/cm^2 for all patients except one patient who received a total of 3.044 joule/cm^2. The maximal recommended limit for UVA in our department is 1.200 joule/cm^2.

The results of therapy are presented in Table I. Adverse effects were erythema (36% of patients), pruritus (20%), and nausea (17%). None of the patients stopped treatment due to adverse effects.

By interviewing 53 patients (90%) by telephone it appeared that the pigmentation after treatment had worsened in 40%. The repigmentation was estimated at the time of the interview, i.e. from 1 to 14 years after PUVA treatment. Before PUVA treatment sunburning was a problem in 92% of the patients, but after therapy it was no longer a problem in 47%. Lingterm effects of skin tumors were not observed by the patients. Regardless of the efficacy of PUVA therapy, 50% of the patients found PUVA were an acceptable therapy. Those who did not appreciate the therapy found it too time-consuming.

DISCUSSION

Previous studies have found that focal vitiligo responds better to PUVA therapy than generalized vitiligo (2, 3), but no clear definition has been given for focal and generalized vitiligo. We found no difference in the treatment efficacy of focal and generalized vitiligo. Nor could we relate specific localizations of vitiligo to the degree of repigmentation. Vitiligo of hands and feet seems however more therapy-resistant than vitiligo in other localizations, as previous studies have demonstrated (2–5).

Table I. *Results of therapy*

	No. of patients	Repigmentation	No. of treatments before pigmentation	Total no of treatments
Localized vitiligo*	1	100%		
	7	75%	17 (5–60)	99 (14–305)
	4	50%		
	7	25%		
	22	No effect	–	33 (5–210)
Generalized vitiligo	0	100%		
	2	75%	13 (4–100)	144 (20–202)
	3	50%		
	2	25%		
	9	No effect	–	59 (6–159)

*Two patients omitted due to lack of information about degree of pigmentation.

We can confirm that it is necessary to give 60–100 PUVA treatments to patients with vitiligo before the effect can be firmly evaluated (2). Table I demonstrates that all patients who did not respond had received approximately 60–100 treatments. Half of the patients mentioned that they could not accept PUVA because it was too time-consuming. It is therefore important to inform the patients about this aspect of PUVA before starting the treatment.

The only effective treatment for vitiligo is at present PUVA. Patients should be well-informed about the length of therapy and the chances for success. PUVA will imply a risk for development of lentigines, actinic keratosis, and squamous cell carcinoma, but not of malignant melanoma. A large study in USA demonstrated a significant increase of skin cancer following PUVA therapy for 3 or more years (6, 7).

We have observed our patients for 5 years following PUVA treatment. At the time of this study we have not found any malignant or premalignant changes in the skin.

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Hemolytic Uremic Syndrome in a Patient with Systemic Sclerosis Treated with Cyclosporin A

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The case is presented of a 48-year-old female suffering from diffuse cutaneous systemic sclerosis (diffuse scleroderma) since 8 years, who went into renal failure as part of hemolytic uremic syndrome following 3 weeks' treatment with 3.8 mg/kg cyclosporin A. Hemolytic uremic syndrome has previously been described in transplant patients receiving cyclosporin A. There are also four cases reported in the literature of renal failure developing in middle aged females with diffuse cutaneous systemic sclerosis after short-term use of low dosage cyclosporin A treatment. It is suggested, that it may be wise not to use cyclosporin A to this category of patients, in which it can not be ruled out, that even a low dose therapy may trigger the rapid onset of scleroderma renal crisis or as in our case provoke hemolytic uremic syndrome.

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Cyclosporin A (CsA), a potent immunosuppressive agent has been claimed to improve severe progressive systemic sclerosis (PSS) (1–6). The drug, however, displays a number of side-effects of which nephrotoxicity and hypertension are considered the most serious (7). Hemolytic uremic syndrome (HUS), which includes anaemia, thrombocytopenia, erythrocyte morphological abnormalities, increased number of reticulocytes, bone marrow hyperplasia, and renal failure have been reported taking place de novo in renal transplant recipients immunosuppressed with CsA (8). Acute renal failure has also been reported in PSS treated with CsA, but it has not been clear whether this was due to treatment or to progression of the disease (2, 5, 9). We present the case of a patient with severe diffuse PSS who developed HUS after only 3 weeks' treatment with CsA.

CASE REPORT

A fourty-eight-year-old female who had diffuse scleroderma for 8 years. Previous treatment with penicillamine from 1983 to 1988 had produced a moderate effect. But after this therapy was discontinued elsewhere, the disease progressed, and treatment with prednisone and methotrexate was given without effect. Due to very severe progression for the last two years methotrexate was discontinued and CsA was started with 3.8 mg/kg. At this time there was symmetrical diffuse involvement of the whole skin of the trunk and extremities with only few lesions of hands and feet, but with pronounced livedo vasculitis on the lower legs together with minor ulcerations. The patient had a decreased passage through esophagus and a tendency to diarrhoea. She had a normal lung function and normal kidney function judged by a normal glomerular filtration rate and a serum creatinine of 87 μmol/l and no proteinuria. A pre-CsA kidney biopsy was considered normal. Her blood pressure (BP) was 120/90.

CsA was administered in two daily dosages (100 + 150 mg) together with nifedipine 10–20 mg and an unchanged prednisone dosage of 10 mg daily. After two weeks' treatment, there were no complaints and blood pressure and serum creatinine remained stable. After four weeks BP had increased to 180/110 and serum creatinine to 177 μmol/l. A proteinuria of 1.0 g/l was discovered and CSA treatment discontinued. One week later BP was still elevated, serum creatinine had increased to 201 μmol/l, thrombocytopenia (64×10^9) and microscopic hematuria had developed. Because of HUS with rapidly deteriorating renal function she was transferred to the department of Nephrology where chronic intermittent dialysis was initiated and total anuria developed within one week. The initial course was complicated by gastrointestinal bleeding from a duodenal ulcer which was effectively treated by electrocoagulation and omeprazol.

A renal biopsy was done 21 days after first sign of renal involvement had appeared.

Signs of haemolysis and thrombocytopenia disappeared within three weeks after start af dialysis. The patients condition stabilized temporarily but renal failure with total anuria persisted. After 4½ month on dialysis death occurred because of a perforated duodenal ulcer and diffuse peritonitis.

PATHOLOGY

The *first renal biopsy* performed just before the beginning of CsA therapy showed a minor degree of interstitial fibrosis and some arterioles with moderate hyalin change, but appeared otherwise normal.

The *second renal biopsy* performed 21 days after the onset of renal involvement consisted of 2 mm medulla and 4 mm cortical tissue.

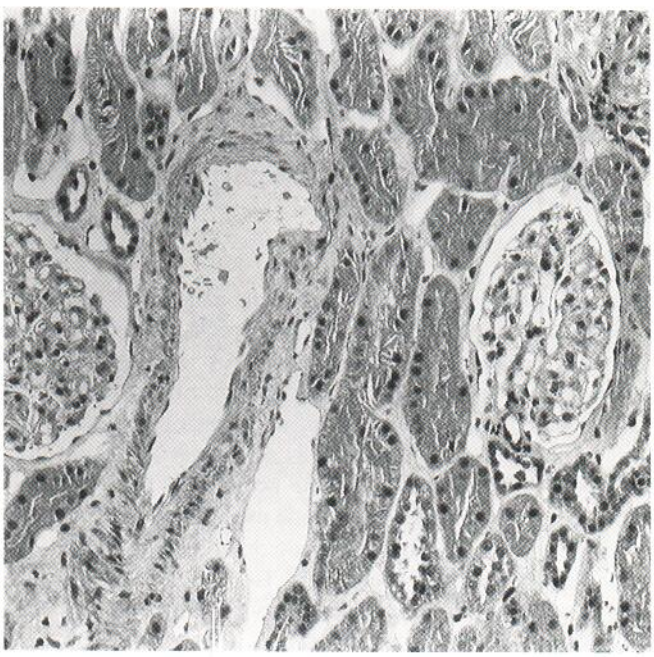

Fig. 1. Renal biopsy performed before cyclosporin treatment. Note the normal structure, particularly the artery. PAS staining, × 150.

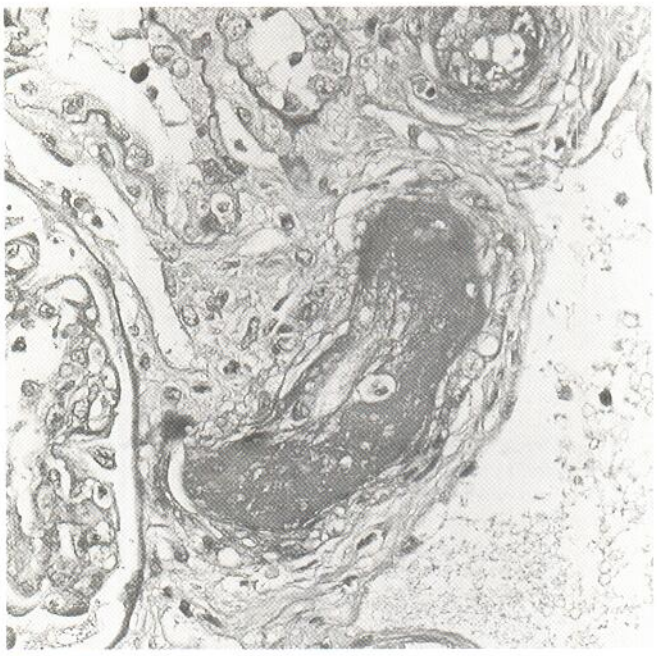

Fig. 2. The second biopsy after 21 days of cyclosporin treatment, during acute renal failure. Arterioles with multilayered, thickened walls and lumen obstructed by thrombi. PAS ×300.

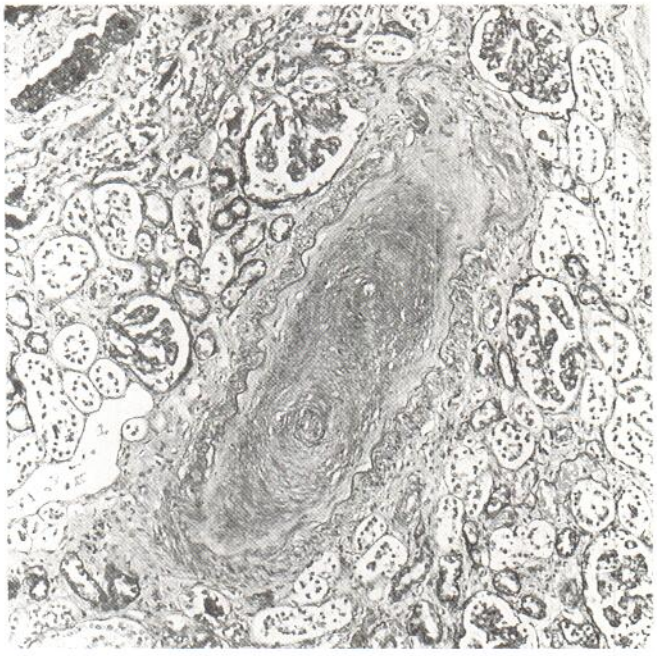

Fig. 3. The kidney at autopsy. Medium-sized artery with concentric, fibrous intimal thickening almost totally occluding the lumen. PAS ×90.

While the medullary part of the biopsy was preserved, most of the cortex showed necrosis of tubular epithelium sparing only a narrow zone close to the medulla. The arterioles were dilated and were occluded by thrombi. Their walls had an onionlike multilayering and had fibrin deposits. Some glomeruli showed ischemic collapse of the tuft, others had thrombosis of some capillary loops. One of them contained an epithelial crescent. A part of one medium sized artery with edematous intimal thickening was present at the edge of the biopsy. The histological diagnosis was thrombotic microangiopathy of the type known from HUS. The necroses were interpreted as indicating bilateral cortical necrosis (focal or complete).

Autopsy. A perforated ulcer was found in the duodenum. There was diffuse peritonitis. The kidneys were moderately reduced in size, smooth, with scattered coarse scars. The cortex was narrowed to 3–5 mm. Microscopically there was moderate interstitial fibrosis and tubular atrophy. Many glomeruli showed ischemic sclerosis of the tuft but no recent capillary thrombosis. In some areas all glomeruli were sclerotic. The arteries showed severe concentric intimal fibrosis with extreme narrowing of their lumina.

DISCUSSION

Our patient developed acute hemolytic anaemia, thrombocytopenia, and acute renal failure only 3 weeks after initiation of CsA 3.8 mg/kg indicating that CsA was responsible to the condition. The renal biopsy performed after the onset of renal insufficiency showed a picture of microangiopathy which has been described in HUS as well as associated to a number of conditions, among them also the acute form of progressive systemic sclerosis (10). Thrombotic microangiopathy has also been described in cyclosporin-treated patients with renal, hepatic and bone marrow transplants. The necrosis present in the second biopsy from our patient led to the assumption of bilateral cortical necrosis. If this has been the case, it must have been of the partial, focal type since the autopsy specimen did not show strong diffuse tubular atrophy. The arterial changes found in the autopsy specimen were of the type well known from the chronic visceral form of progressive systemic sclerosis. Our interpretation of these findings is that an acute phase of visceral sclerodermia evolved possibly due to the cyclosporin-treatment, initially with severe microangiopathy which eventually led to severe arterial changes characteristic of chronic visceral sclerodermia. Cortical necrosis, which must have been patchy, played probably a minor role in the renal insufficiency.

Patients with a high risk of renal failure from PSS are mainly middle aged females with a disease history of approximately 2 to 3 years. A rapid increase in the generalized cutaneous sclerosis may precede the renal failure (11). Although our patient had a PSS history of 8 years, she had only severely progressed for the last 2 years and therefore still should be considered belonging to the risk group.

The previous reports (2, 5, 7) on renal failure following CsA in PSS also all concern the risk group of middle aged females suffering from diffuse scleroderma (diffuse cutaneous systemic sclerosis). In all four patients low dosage therapy was used and the renal failure occurred after a few months of treatment. Two patients, however, were treated with NSAID's simultaneously, which may increase toxicity of CsA. This was not the case in our patient. A renal biopsy was performed in one of these patients showing recent thrombotic microangiopathic lesions, ischemic glomeruli, moderate tubular atrophy, and interstitial fibrosis. No pretreatment kidney biopsies were reported and no histories of HUS were disclosed.

The nephrotoxicity of our patient should not be confused with the low grade morphological changes of arteriolar hyalinosis and interstitial fibrosis previously reported by us to follow low dosage CsA in PSS (1). These latter findings are similar to changes taking place in psoriatic patients treated

with the same low dosage CsA for approximately one year (12). The clinical relevance of these minor changes is still unknown, and in our opinion they do not exclude the use of CsA in severe psoriasis or in aggressive PSS outside the risk group, when found necessary. We do, however, find it is prudent not to use CsA in female patients with diffuse PSS as long as it can not be ruled out, that CsA even in a low dose regime may trigger the rapid onset of a renal crisis. It is also important to state, that CsA should not be combined with NSAID's in PSS treated with CsA.

HUS has also been found in other conditions i.e. in CsA-treated patients who underwent bone-marrow transplantation (13). The pathogenesis of the CsA induced HUS is unknown. Leithner and coworkers (12) proposed that CsA precipitates HUS by inhibiting prostacyclin synthesis by vascular tissue. The reduced PGI_2 should lead to endothelial cell damage, capillary thrombosis and vessel wall necrosis. It has also been suggested that this CsA reaction is idiosyncratic and not dose related (8). In our case CsA was immediately discontinued after diagnosis. But renal failure progressed to total anuria necessitating chronic dialysis. The patient eventually died after 4½ months on dialysis from a perforated duodenal ulcer.

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Acta Derm Venereol (Stockh) 1992; 72: 310–311

Escherichia coli Cellulitis: Two Cases

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We report two cases of cellulitis of the legs occurring in adults where *Escherichia coli* (*E. coli*) was, or probably was, the causative bacterial agent. *E. coli* and other gram-negative bacilli cellulitis are rarely reported. However, in cellulitis, the causative microorganism is rarely identified, and some cases of *E. coli* cellulitis could be unrecognized. Furthermore, classical risk factors for gram-negative sepsis are characterized by a state of leucocyte dysfunction which could explain the possibility of a severe, even lethal, course of gram-negative cellulitis. Therefore, the occurrence of cellulitis in patients with risk factors should prompt attempts at isolating the pathogenic microorganism, and a broad spectrum of antibiotic therapy should be initiated. ***Key words: Necrotizing cellulitis; Gram-negative cellulitis; Soft-tissue infection; Erysipela; Fasciitis.***

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Cellulitis is an acute spreading infection of the skin extending deeper than erysipelas to involve the subcutaneous tissues (1). In adult cellulitis, the causative bacterial agent is rarely identified even when fine needle aspiration and culture of cutaneous biopsies are performed. However, β-hemolytic *Streptococcus* group A is thought to be the responsible bacteria in the majority of cases, especially because cellulitis is usually cured with penicillin G (1). Furthermore, an immunohistological study of skin biopsies from cellulitis has shown that streptococcal antigens are present, even when *Streptococcus* itself cannot be isolated (2). Other bacterial agents are sometimes encountered, such as other streptococcal groups or *Staphylococcus aureus*, but *Escherichia coli* (*E. coli*) cellulitis seems to be exceptional.

We report two cases of *E. coli* cellulitis occurring in adults. Presence of risk factors for gram-negative bacteria (GNB) sepsis, leading to a state of immunodeficiency, could account for the severity of the cellulitis, more than the bacteria.

CASE REPORT

Case 1. A 77-year-old woman was seen with a 72-h history of fever (38°C) and bilateral inflammatory edema of the lower legs. She had a past medical history of leg ulcer secondary to a superficial venous insufficiency with varicosae and statis pigmented dermatitis. She had also recently had a hepatitis C post-transfusional liver cirrhosis complicated with hematemesis due to esophagal varices.

At examination she was confused and her temperature was 39°C. She had a necrotizing cellulitis of the lower legs: both limbs were swollen, erythematous, with bullae, pustules, ulcerations and necrosis. There were a hepatomegaly, a collateral abdominal wall circulation and a splenomegaly. The white cell count was 20,000 with 90% neutrophils. Hemostasis tests showed a hepatocellular insufficiency and a disseminated intravascular coagulation: the fibrinogen was 1.7 g/l, the platelet count was 60,000, the thromboplastin time ratio was 2, the coagulation factor V was decreased at 56% of normal. A test for fibrin-split products was negative, but soluble complexes were present. Serum electrolytes and renal function were normal. *E. coli* was isolated from 3 blood cultures, blister fluid, fine needle aspiration from cellulitis and skin biopsy. No associated bacterial agent was found. Skin biopsy showed a massive polymorphonuclear infiltrate in the dermis and subcutaneous tissue, with presence of fibrinous thrombi in the vascular lumen. A treatment was administered intravenously with pefloxacine (400 mg b.i.d.) and amoxicillin-clavulinic acid (1 g × 4 times a day). The patient was less ill and afebrile after 24 h. A surgical debridement was performed, but after an initial clinical and biological improvement, local signs worsened despite antibiotic treatment, requiring a second surgical debridement. Subsequently, the hepatocellular insufficiency worsened and the patient died.

Case 2. A 72-year-old man presented with an erysipelas-like cellulitis of the left lower leg which had started 3 days earlier. On examination, he had a swollen leg with diffuse erythema, tenderness and warmth. There was a left inguinal inflammatory lymph node. The patient's temperature was 39°C, with shivers and sweatings, and he appeared acutely ill. There was a small traumatic skin erosin on the internal aspect of the left ankle that had not healed for 1 month. There was a superficial venous insufficiency. He was an alcoholic and a smoker. The physical examination was otherwise normal. Specimens of blood, fine needle aspiration, and a swab from the ankle erosin were obtained for culture. The white cell count was 11,000 with 63% neutrophils. The hepatic tests were normal. The glucose was 7.6 mmol/l at admission but became spontaneously normal. The antibodies to streptococcal exoenzymes were negative at admission and 2 weeks later. Intravenous oxacillin (6 g per day) was started. Forty-eight hours later, local and general signs worsened and the temperature remained high. Three blood cultures were positive for *E. coli* and the antibiotic regimen was modified for amoxicillin (9 g per day) and dibekacine (225 mg per day). The cultures of swab, fine needle aspiration and skin biopsy specimens were sterile. The search for another site of infection than skin remained negative: a urine culture performed before antibiotics was sterile, a stool culture was normal, a colic roentgenogram and ultrasonographic scan of the abdomen were normal.

Seventy-two hours later the patient felt better, but the temperature was still 38°C for 7 days and the leg remained erythematous for 10 days. Six months later the patient was seen in good health, with total healing of his lower leg.

DISCUSSION

We have reported two cases of cellulitis of the lower legs where *E. coli* was or was suspected to be the causative bacterial agent. In the first case, *E. coli* was cultivated from the blood, the cutaneous blisters, skin aspiration, and cutaneous biopsy. In the second case, despite the lack of positive culture from the skin, the role of *E. coli* is more than putative since it could be isolated from 3 blood cultures and because the cellulitis was not improved with oxacillin therapy but was secondarily cured with amoxicillin treatment.

E. coli cellulitis seems to be rare. In adults, only one case of

perianal cellulitis due to both *E. coli* and *Morganella morganii* has been reported (2). In children five cases of *E. coli* cellulitis have been reported (3, 4). All had a corticodependent nephrotic syndrome. Other GNB have been occasionally reported as causative for cellulitis in adulthood (5, 6, 7, 8). In necrotizing cellulitis, GNB are more frequently isolated, but almost exclusively in association with gram-negative or anaerobic bacteria (9, 10). In these cases, whether GNB are secondarily present or causative agents is unclear.

Nevertheless, the rarity of *E. coli* cellulitis must be cautiously interpreted for several reasons. First, in the majority of cases of cellulitis, no causative infectious agent can be found (1). Second, in the published cases of GNB cellulitis, as in our cases, the clinical features are unremarkable and impossible to distinguish from streptococcal cellulitis. Third, some of the GNB cellulitis might be cured with an empiric antibiotic treatment. Thus, it is possible that some of the *E. coli* or other GNB cellulitis remain unrecognized.

Although empiric treatment could cure some of the GNB cellulitis, *E. coli* and other GNB cellulitis seem to have a high risk of severe evolution, as our first case. It is uncertain whether such an evolution is due to the infectious agent itself: GNB cellulitis can have a favorable course despite the absence of surgical treatment, whereas *Streptococcus* remains the main etiologic agent of necrotizing cellulitis and fasciitis (9, 10). Presence of risk factors for GNB sepsis, neutropenia, diabetes mellitus, renal insufficiency, hepatocellular insufficiency, corticosteroid treatment, and chronic alcohol consumption (5) are characterized by a state of functional deficiency of polymorphonuclear cells, leading to a defect in the non-specific inflammatory reaction which seems to have a major role in the healing process of cellulitis (11). Presence of risk factor for GNB sepsis could explain the high risk of severe evolution of GNB cellulitis. Thus, when one of these risk factors is present, it is important to try to isolate the causative agent(s) by fine needle aspiration and culture of cutaneous biopsy sample, even if its yield is usually low, in order to avoid delay in effective treatment. Indeed, it has been claimed that in patients with an underlying disease associated with immunologic dysfunction, microbiologic evaluations of cutaneous cellulitis yield pathogenic organisms at a low but tangible rate (11). Moreover, in these cases, the antibiotic regimen should not be penicillin G or oxacillin: the chosen antibiotic should have a wider spectrum as for example the combination amoxicillin-clavulinic acid. An early well-adaptated antibiotic treatment is probably the best way to prevent necrotizing evolution and fascial spreading of an infectious cellulitis.

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LETTERS TO THE EDITOR

Prophylactic Antibiotics for Skin Surgery?

Sir,

We read with interest the report by Maurice et al. on the need for prophylactic antibiotics in skin curettage (1). An increasingly elderly population with a greater prevalence of skin tumours (2) and the impact of United Kingdom health reforms, encouraging skin surgery by primary care physicians (3), have caused an expansion of dermatological procedures. Given the potentially catastrophic consequences of bacterial endocarditis, the need for prophylactic antibodics in skin surgery should not be dependent on "an educated guess" (4).

Although two studies have investigated the incidence of bacteraemia associated with skin surgery, both were conspicuous by their small sample size (5, 6) and to extrapolate to populations on this basis may be misleading.

Maurice's investigations identified coagulase-negative staphylococcus as the predominant organism, present on 69% of skin lesions and therefore the most likely cause of bacteraemia and possible endocarditis (1). We were surprised that amoxycillin was suggested as a suitable prophylaxis in patients at high risk of endocarditis. We have reviewed the sensitivities of coagulase-negative staphylococcal blood culture isolates, collected over the past 5 months in this hospital. Of 115 isolates just 11% were sensitive to amoxycillin (Table I). The only antibiotic to which all were sensitive was vancomycin. Vancomycin must be infused intravenously over an hour, to minimize the risks of hypotension and rash (7).

Table I. *Sensitivities of Staphylococcus epidermidis blood culture isolates*

Antibiotic	No of isolates	
	Resistant	Sensitive
Penicillin/Amoxycillin	103	12
Flucloxacillin	77	38
Erythromycin	71	44
Gentamicin	54	61
Rifampicin	2	113
Vancomycin	0	115

The incidence of bacteraemia associated with skin surgery needs to be more precisely defined so that the benefit of an adequate antibiotic prophylaxis can be balanced against the inconvenience and potential morbidity of such a regimen.

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Response to the Letter by Carmichael et al.

It was an oversight on our part that we used in the last paragraph of our paper "amoxycillin" rather than "antibiotic" because we too noted that most of the coagulase-negative staphylococci isolated from the skin lesions in our study were resistant to penicillin/amoxycillin. We agree that vancomycin would be the logical choice in the very few instances where prophylaxis is indicated and also agree that more information is required to assess the risks.

P. D. L. Maurice, S. Parker, B. S. Azadian and J. J. Cream, Department of Dermatology, Charing Cross Hospital, London, United Kingdom.

HIV Infection and Loss of Treponemal Test Reactivity

Sir,

We read with great interest the article by Sjövall, Flamholc, Kroon and Bredberg (Acta Derm Venereol (Stockh) 1991; 71: 458), in which they reported on a 34-year-old man, HIV positive, who initially presented in 1986 with secondary syphilis and high antibody titers for Wasserman complement fixation, VDRL, TPHA, FTA-abs and TPI. He later developed AIDS after Wasserman, VDRL, TPHA and TPI turned out to be negative. The authors concluded that the seroreversal in this patient was not due to a serious humoral derangement caused by HIV and/or the medications prescribed; the authors stressed the fact that treponemal tests are unsensitive markers of previous syphilis infection. We would like to share with the readers of the journal a different experience with serological tests for syphilis(STS) in HIV-infected patients. Recently, we studied a group of 268 patients that were followed up prospectively and screened for syphilis (history, clinical, TPHA, FTA-abs, VDRL) at the entry and every 6 months between 1986 and 1990; most were males (239), mainly CDC stages II (184) and III (75). One hundred and thirty-four had either history of syphilis (125) or positive STS (9) at the initial visit. Fifteen patients seroreverted before entry and 119 tested were positive at the initial visit. Fourteen IVDU with false VDRL were excluded. Fifteen patients had high titers of antibodies at the initial visit (of whom 10 had documented recent syphilis). Fifty-five patients with STS returned for follow-up, of whom only 6 increased their STS titers (3 with clinical syphilis, and 3 possible seroreactivation). Only 7 patients had a negativation of one of the tests (FTA 7, VDRL 7, TPHA 1) and 42 had no modification or a very slight decrease of their titers, after a mean follow-up of 3.3 years, the CD 4 count decreasing concomitantly from 628 to 336/mm^3. In the vast majority of cases the kinetics of STS were perfectly regular and reliable, and only once did we notice a negativation of the TPHA. Negativation of the treponemal tests thus appears a very rare event in the course of syphilis occurring in patients infected by HIV.

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Response to the Letter by Puppin et al.

With great interest we have studied the data presented by Douglas Puppin Jr and associates, demonstrating that 7 out of 55 (13%) HIV-positive patients lost their reactivity to a treponemal test and concluding that this is a very rare event. In this context, the report by Haas et al. (1) is relevant, showing a seroreversal frequency of 38% during symptomatic HIV infection (in 6 cases FTA-abs and in 7 cases TPHA became negative). Previously, it has been generally believed that such treponemal test seroreversals do not occur. To summarize, in our opinion it is now clear that treponemal tests during HIV infection no longer can be regarded as sensitive markers of previous syphilis infection.

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A High Incidence of Venereal Diseases and a Rapid Increase of Herpes Zoster in Africa

Sir,

From 1969–1973 I was the advisor to the government in Uganda for dermatology, venereology and leprosy. With systematic darkground microscopical examination of all genital sores for *Treponema pallidum* and microscopical examination of all patients with discharge for *Neisseria gonorrhea* we found a very high prevalence of venereal diseases. The last year we established in addition an effective laboratory for serological testing for syphilis and culturing for gonococci with determination of the resistant pattern.

My statistics for 1973 showed 19,000 cases of gonorrhea, 2,000 cases of early contagious syphilis, 40 cases of early congenital syphilis, 1,000 cases of chancroid and 50 cases of lymphogranuloma venerium. This represented presumably only one third of patients in Kampala (350,000 inhabitants) and its nearest surroundings (1).

We found that contact tracing was feasible but insufficient in view of the high prevalence. The patients, however, attended with impressive regularity for treatment and our treatment results were satisfactory.

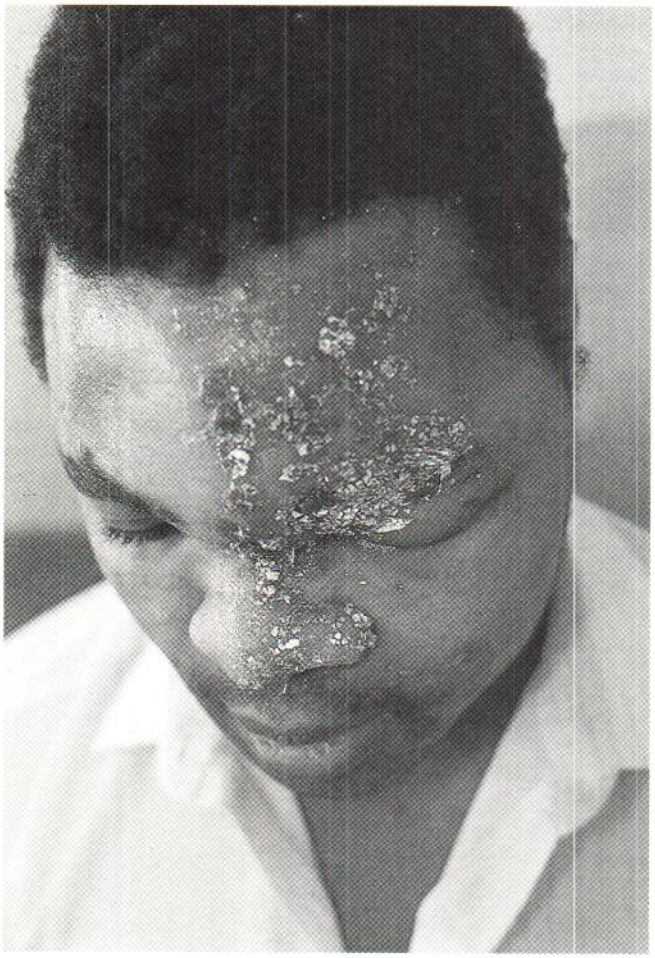

Fig. 1. Severe necrotic herpes zoster in a young man from Malawi.

During 1973 we diagnosed, however, only 10 cases of herpes zoster in Uganda.

When I retired from my last post in Scandinavia in 1984, I returned to Africa as the only dermatologist to Malawi, the former Nyasaland. In 1986, 133 cases of herpes zoster were seen (2). The Danish Red Cross has since my departure taken over the clinic and the number of new patients attending the clinic and the four district clinics has increased from 22,000 in 1986 to 37,000 in 1990 (3). In 1990 the number of herpes zoster showed a disproportionate increase to 840.

The patients were mainly young men with extensive, crusted and partly necrotic facial herpes zoster (Fig. 1). This increase of herpes zoster in young adults is remarkable. Without doubt this is related to HIV on the African continent (4). HIV was not recognized anywhere during my stay in Uganda and in retrospect I do not remember any case with the known symptoms of AIDS. This suggests that HIV infection is a new disease also in Africa.

The prevalence of HIV in Malawi is not known – lack of screening kits is one of the difficulties. Surveys from antenatal clinics and among blood donors have shown figures as high as 18% (5).

Unable to offer any treatment or psychological or psychiatric support, I thought it acceptable not to inform the patients, wishing not to worry them.

Since my departure several patients with seborrheic dermatitis and psoriasis have developed AIDS (3).

The aim of this report is to call attention to the high prevalence of venereal diseases in Central Africa and the marked increase of herpes zoster among young adults from 1972 to 1990. This indicates that the HIV infection is a new event in Africa.

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