

## CORRESPONDENCE

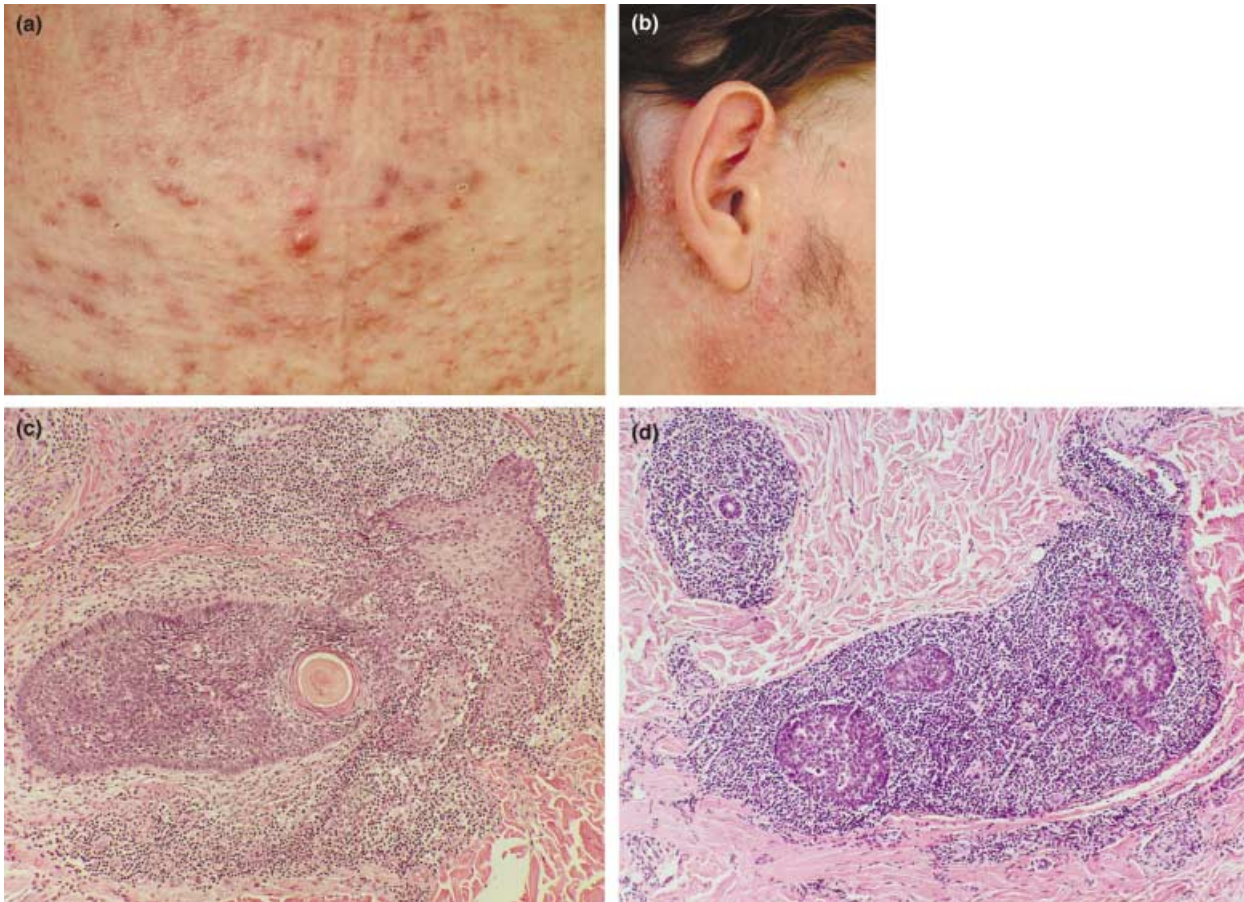
### An unusual variant of granulomatous adnexotropic cutaneous T-cell lymphoma

SIR, A 40-year-old man reported the slow progressive appearance, during the previous 6 years, of pruritic erythematous lesions on the trunk, buttock, abdomen, axilla, genital area and forearm (Fig. 1a). Lesions consisted of follicular papules, comedones, milia and cysts. Lesional areas were alopecic (Fig. 1b), and diffuse alopecia was also present on the scalp and beard area, along with comedones and cysts. The patient reported severe skin dryness, especially in the involved areas. No impairment of salivary or lacrimary function was noted. Serological and haematological tests were all normal or negative.

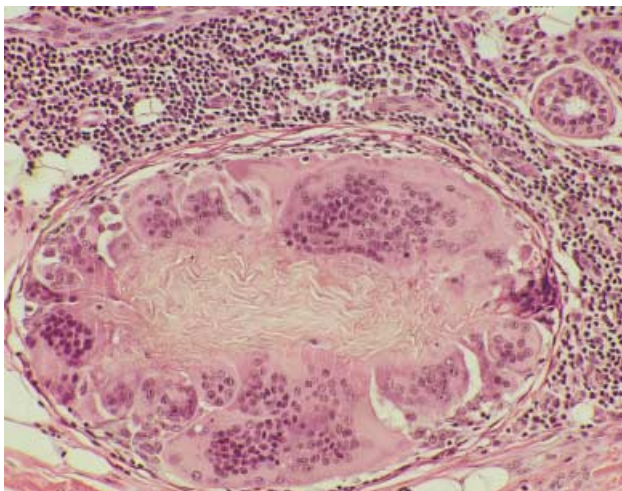
Because of the diffuse presence of cysts and comedones, a diagnosis of chloracne had been made in another institution;

the clinical diagnosis was confirmed histologically by the presence of infundibular cysts and a granulomatous foreign body reaction to keratin scales.

A further biopsy was performed: the most striking histological feature was a lymphocytic infiltrate involving eccrine glands and coils along with a characteristic epithelial hyperplasia (Figs 1c,d). This picture fits perfectly with that reported in the literature<sup>1–3</sup> as being characteristic of syringolymphoid hyperplasia, also known as syringotropic mycosis fungoides or syringotropic cutaneous T-cell lymphoma (CTCL). The hair follicles were involved by the lymphocytic infiltrate in a manner similar to that of the eccrine glands. Follicles were surrounded by a dense lymphocytic infiltrate, with extensive exocytosis. Occasional Pautrier microabscesses were evident in the follicular sheath. This pattern is that of pilotropic mycosis fungoides, a form of folliculotropic CTCL.<sup>4–8</sup> Many follicles were entirely trans-



**Figure 1.** (a) The clinical picture was characterized by erythematous plaques mostly located on the forearm, abdomen, buttock and scalp. Plaques were scattered, with follicular papules, cysts, milia and comedones. (b) Alopecia, along with cysts and comedones, was an important clinical feature, with anhidrosis in the involved areas. (c, d) Histologically, almost all the eccrine glands and hair follicles in the specimens were surrounded by a dense lymphocytic infiltrate. Exocytosis of lymphocytes within the epithelia was present, along with Pautrier-like microabscesses. Epithelia underwent a peculiar basal cell hyperplasia, resulting in a cribriform spiroadenoma-like or basaloid pattern (haematoxylin and eosin; original magnification  $\times 132$ ).



**Figure 2.** The granulomatous reaction was usually related to a large amount of keratin released by follicles and cysts. In a few areas the granulomatous foreign body reaction overwhelmed other pathological findings (haematoxylin and eosin; original magnification  $\times 132$ ).

formed into bizarre undifferentiated basaloid structures<sup>5</sup> resembling a neoplasm with follicular differentiation, such as basal cell carcinoma, trichoblastoma or cutaneous lymphadenoma. Numerous infundibular cysts were present, scattered throughout the specimens.

A granulomatous foreign body reaction was evident in some sections (Fig. 2), and was prevalent in one of the biopsies, where it constituted the main pathological alteration. Granulomas were closely related to the adnexal structures, both follicular and glandular. Most of the granulomatous reactions seemed to be associated with the hair follicles, ruptured follicular cysts or comedones. The centre of the granulomas contained a roundish collection of keratin scales, which evidently elicited the inflammatory process. Occasionally the granulomatous infiltrate was diffuse and the histiocytes and giant cells were mingled with keratin scales. A few small granulomas were located within the eccrine lobules involved by the syringolymphoid process. We cannot explain the presence of keratin in the eccrine lobules, and were unable to attribute it to squamous metaplasia of eccrine glands. The exact nature and cause of this finding remain unresolved.

Almost the entire lymphocytic infiltrate was CD4 positive; only very rare cells were CD8 positive. Staining for the B-lymphocytic line of differentiation was negative. L.Cerroni (University of Graz, Austria) performed a molecular analysis<sup>4</sup> that provided evidence for a clonal biallelic rearrangement of the T-cell receptor gamma chain gene.

The patient refused the suggested radiotherapy and psoralen plus ultraviolet A therapy. Standard therapy with interferon alfa (IntronA<sup>®</sup>, 3 million units three times weekly; Schering-Plough, Segrate, MI, USA) plus acitretin 25 mg daily was undertaken. An improvement in sweat function

and a reduction in the size and number of cysts and comedones was noted.

In our case we found features of syringolymphoid hyperplasia, an eccrine gland-centred CTCL, combined with features of folliculotropic mycosis fungoides, a hair follicle-centred CTCL. Besides these adnexal changes, a strong granulomatous reaction was present involving both follicular and eccrine structures. This inflammatory reaction occasionally overwhelmed all other morphological details, and was misleadingly suggestive of a granulomatous nonneoplastic process.

Our case demonstrates that syringolymphoid hyperplasia with alopecia (syringotropic CTCL) can present with follicular involvement, resulting in a peculiar clinical and pathological profile. Follicular involvement can be devoid of mucinosis and characterized instead by the transformation of the follicles into basaloid undifferentiated structures, along with the production of cysts and comedones, as in follicular mycosis fungoides (pilotropic or folliculotropic CTCL). This combined eccrine and follicular lymphocytic involvement and epithelial hyperplasia indicates that CTCL/mycosis fungoides may interact at the same time with follicular and eccrine adnexa, and can elicit the conversion of these adnexa into peculiar, undifferentiated, 'hyperplastic' epithelial structures. Because of these aspects, the term adnexotropic CTCL is probably the most appropriate one for this and other related lesions.

The peculiar granulomatous component present in our case indicates that the adnexal involvement can cause the production of large amounts of keratin which, dispersed in the dermis, triggers a strong inflammatory foreign body reaction. This aspect can be so diffuse and prevalent that the true neoplastic nature of the process may easily be missed, as in our patient, where an incorrect diagnosis of reactive inflammatory reaction was, quite reasonably, sustained for years.

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### Comparison of melanocytic naevi with photographs, a recommended method

SIR, For many years now there have been public health concerns in many countries about increasing mortality rates due to melanoma. Part of the approach to early diagnosis has been to encourage people at high risk, particularly those with a very large number of melanocytic naevi, to have standardized photography and to practise skin self-examination using the photographs as a template. Medical practitioners also use the photographs during routine surveillance of these patients.

However, there is a dearth of standardized instructions and research on how to use these photographs. Anyone working with patients with large numbers of melanocytic naevi will appreciate how difficult it is to compare lesions on photographs to the same lesions on the patient's skin.

The prints are generally small and the lighting used when they are photographed is generally quite different to the incandescent lighting used at home or in clinics when comparing the skin with the photographs. The very large number of lesions people have, for which the use of photographs is normally promoted, may require hours for spot-by-spot comparison from photographs to the skin.

It has become clear from our experience at the Skin and Cancer Foundation of Victoria, where we follow up many patients with standardized photography, that a spot-by-spot comparison is not the way these photographs should be used. We recommend that patients or physicians using these photographs should compare a group of spots on the photograph with the same group of spots on the skin. Looking for a change in size, shape or colour in a lesion compared with a group of surrounding lesions when examining the skin and comparing with the photographs is recommended. Using a group of lesions allows the eye to balance for the different lighting conditions in a clinic or during skin self-examination. It also makes it very easy to say that there has been a change in size, shape or colour of an individual lesion compared with those around it.

It is surprising how astute the eye/brain is at detecting differences by comparison with surrounding objects when comparing two very similar images. That is the basis for the children's puzzles where they are asked to record how many differences they detect between two copies of a drawing where some minor changes have been made in one of the copies.

I recommend this technique to your readers. It could be that this is the way that dermatologists are using these photographs subconsciously already. However, there is no real evidence base published on this approach. I therefore suggest also that here is a small research project for someone in the future. A controlled comparison of using photographs of both single and grouped lesions could be performed with both the clinicians and patients using them in the assessment of their value. Ironically, it has been noted in the past in a survey of the public's knowledge about melanoma that they say that they just look different to surrounding lesions.<sup>1</sup>

If research did confirm my suggestion, this approach will not only reduce the time required to use the photographs, but also, ideally will increase the specificity and sensitivity of the technique by making it more akin to what we do in the visual inspection of things around us in our everyday life.

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### Antibiotic-resistant *Propionibacteria acnes* may not be the major issue clinically or microbiologically in acne

SIR, Coates *et al.*<sup>1</sup> have performed a definitive study documenting the prevalence of antibiotic-resistant *Propionibacteria acnes* on the skin of acne patients in the May issue of the *British Journal of Dermatology*. However, we query whether there might be more flexibility in some of their premises. More specifically, we question whether reduction of the numbers of *P. acnes* directly correlates with clinical success as no correlation between resistance and therapeutic outcome were provided in this study. Thus, antibiotic resistance may not necessarily compromise therapeutic outcomes. We propose the microbiological principle of biofilms might apply to acne in which alteration of the physical, biological, and chemical environment of the pilosebaceous unit may be the primary function of antibiotics and other acne therapies.<sup>2</sup>

Realistically, *P. acnes* probably do not live as plankton, or free-floating microorganisms in suspension within the pilosebaceous units, but as biofilms. As such, a complex of bacteria anchored to an internal surface of the pilosebaceous unit, enveloped by an exopolysaccharide matrix produced by these microorganisms, obtain protection from the host immune system and antibiotics. Indeed, microbial biofilms are a common cause of persistent infections,<sup>3</sup> such as otitis media<sup>4</sup> and dermatophytomas of the nails.<sup>5</sup>

Within a biofilm, multiple microenvironments exist allowing for the same species of bacteria to live in diverse niches with varying rates of metabolism, replication, and responsiveness to antibiotic therapy. Indeed, microorganisms within biofilms are found to be 50–500 times more resistant to antimicrobial therapies than free-floating (planktonic) bacteria.<sup>6</sup> This may explain the observation of more resistant strains of *P. acnes* on the skin surface than in the pilosebaceous follicle. Bacteria in a biofilm have a natural antibiotic resistance not apparent on agar plates. Regardless of therapeutic modalities, *P. acnes* is always found within the pilosebaceous unit, and the number of organisms does not necessarily correlate with clinical results. *P. acnes* is not pathogenic by normal standards, as a correlation has never been shown between the number of bacteria and severity and type of acne.

Thus, applying the concept of biofilms to acne, antibiotic resistance in standard bacterial cultures is no longer a reliable assessment of treatment outcome. It replaces the authors' stated confusion concerning the complexity of the relationship between resistance and response in acne, with a myriad of other biological and chemical queries. It also naturally leads to the development of additional acne agents, such as the formation of benzoyl peroxide radicals, which may make a more significant alteration to the microenvironment in which the *P. acnes* reside.<sup>7</sup> With our present state of knowledge, antiacne antibiotics should be evaluated based on clinical outcome, not on the unnatural resistance patterns of planktonic, agar-grown, *P. acnes*.

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## Propionibacterial biofilms cannot explain antibiotic resistance but might contribute to some cases of antibiotic recalcitrant acne

SIR, Antibiotic resistance is defined as a change in susceptibility of a microorganism to an antibiotic such that a higher concentration of drug is required to inhibit growth of a resistant strain compared to a fully susceptible wild type strain. In our previous work we have defined resistance using laboratory criteria in that the minimum inhibitory concentrations (MICs) of drugs for resistant strains of *Propionibacteria acnes* and *P. granulosum* exceed those of fully susceptible strains. We have gone on to determine the molecular genetic basis of this 'acquired' resistance to erythromycin, clindamycin and tetracycline and have shown that it is mainly due to point mutations in the target site (ribosomal RNA). However, we concede that resistance defined using laboratory criteria may not be clinically relevant. Here the question is whether the MIC of the drug for the organisms exceeds concentrations that can be achieved therapeutically at the site of action. In the case of acne there are two sites that are relevant: the skin surface (from which previously sterile follicles can become infected) and the ducts of pilosebaceous follicles, both normal and lesional. Many years ago we showed that patients colonized with erythromycin-resistant propionibacteria responded inadequately (< 50% improvement) to oral erythromycin therapy.<sup>1</sup> In this scenario, there is absolutely no possibility that resistance is not clinically relevant; MICs of erythromycin for resistant strains (512–2048 µg mL<sup>-1</sup>) are at least 100 times higher than plasma levels on a dose of 1 g day<sup>-1</sup>.

In the case of tetracyclines, proving a link between resistance and treatment outcomes is much harder because MICs of resistant strains (4–64 µg mL<sup>-1</sup> for tetracycline and 2–16 µg mL<sup>-1</sup> for minocycline) overlap with plasma levels so that the actual concentration achieved in individual follicles is critical. In acne, each follicle behaves like a separate infection, and the response of each lesion is independent of all the others. What matters is whether the concentration in each follicle exceeds the MIC of the drug for the bacterial population within that follicle. Some follicles will be colonized only with susceptible bacteria, others only with resistant bacteria and yet others with a mixture of both. In addition, drug levels will in all likelihood vary in relation to sebum excretion rate, so it is easy to appreciate that there is no simple relationship between resistance and outcomes except in the case of oral erythromycin.

So what would be the effect of propionibacterial growth in biofilms upon response to antibiotics? Burkhart and Burkhart<sup>2</sup> are right in saying that many antibiotics penetrate biofilms poorly and that clinical resistance may arise from an inability of antibiotics to reach bacteria growing in

biofilms. However, we know that in acne this cannot be the case generally. There are ample data showing >90% reductions in viable propionibacteria in patients treated with all the classic antiacne antibiotics except topical clindamycin. Bacteria that have not been exposed to selective pressure do not become resistant, thus the very fact that propionibacteria have acquired resistance despite having no pre-existing pool of mobile resistance genes shows that they have been subjected to a very considerable degree of selective pressure arising from the extensive use of antibiotics to treat acne.

Whether antibiotic resistance in *P. acnes* is clinically relevant is not the only consideration. Long-term antibiotic use also has effects on other non-target commensal and semicomensal bacteria such as streptococci, coagulase negative staphylococci and *Staphylococcus aureus*. These organisms have the potential both to be pathogenic and to exchange mobile resistance elements with classically pathogenic related organisms such as *Streptococcus pyogenes*. We should try to steer away from the use of long-term antibiotics as a matter of principle so as not to promote increased carriage of resistant organisms with pathogenic potential. Evaluating antiacne antibiotics on clinical outcomes alone ignores this important aspect of risk benefit, resistance being the only communicable adverse drug reaction.

Assuming biofilms contribute significantly to clinical resistance to antibiotics this would have been evident since antibiotics were first used to treat the disease; we would not expect to see any change over time. Indeed there are patients who fail to respond adequately to antibiotics and there are many reasons why this might be the case. Any role of biofilms is not likely to operate at the level of individual patients but at the follicular level. Biofilms may explain why antibiotics work less well *in vivo* against resistant and susceptible propionibacterial strains that *in vitro* results would predict. *In vivo*, no antibiotic-based regimen reduces propionibacterial numbers as well as benzoyl peroxide and yet MICs of antibiotics for susceptible strains *in vitro* are at least an order of magnitude lower.<sup>3</sup> This observation suggests that something interferes with the action of antibiotics *in vivo* or that the action of benzoyl peroxide is potentiated. Biofilms may explain why it is so difficult to eradicate propionibacteria from their niche.

We note with interest two recent reports that production of the polysaccharide intercellular adhesin, essential for biofilm formation by *Staphylococcus epidermidis*, is promoted by exposure to alcohols, common components of topical antibiotic formulations for acne.<sup>4</sup> This observation suggests that these and other vehicle components may affect interactions between resident bacterial communities *in vivo*.

Burkhart and Burkhart are right to raise the issue of propionibacterial biofilms as they may not only affect responses to antibiotics but may also interfere with the immune response by sequestering organisms in a protected environment. Therefore we look forward with interest to the

outcome of their investigation of propionibacterial biofilms and their role in the pathogenicity of acne.

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## Squamous cell carcinoma in a patient with non-bullous congenital ichthyosiform erythroderma

SIR, Non-bullous congenital ichthyosiform erythroderma (NBCIE) is a rare autosomal recessive disease characterized by hyperkeratosis and generalized erythema from birth. Although there are some reports concerning skin cancers associated with congenital ichthyoses including ichthyosis hystrix,<sup>1</sup> Netherton's syndrome,<sup>2</sup> KID syndrome<sup>3</sup> and MAUIE syndrome,<sup>4</sup> the occurrence of squamous cell carcinoma (SCC) in NBCIE has not been reported in the literature, as far as we know. We report here a Japanese male with NBCIE who exhibited SCC on his neck.

A 44-year-old Japanese man has been seen for 28 years in the Department of Dermatology, Hokkaido University Graduate School of Medicine. He had been suffering from NBCIE since birth. He had been treated with oral etretinate, 10 mg daily, for about 20 years.

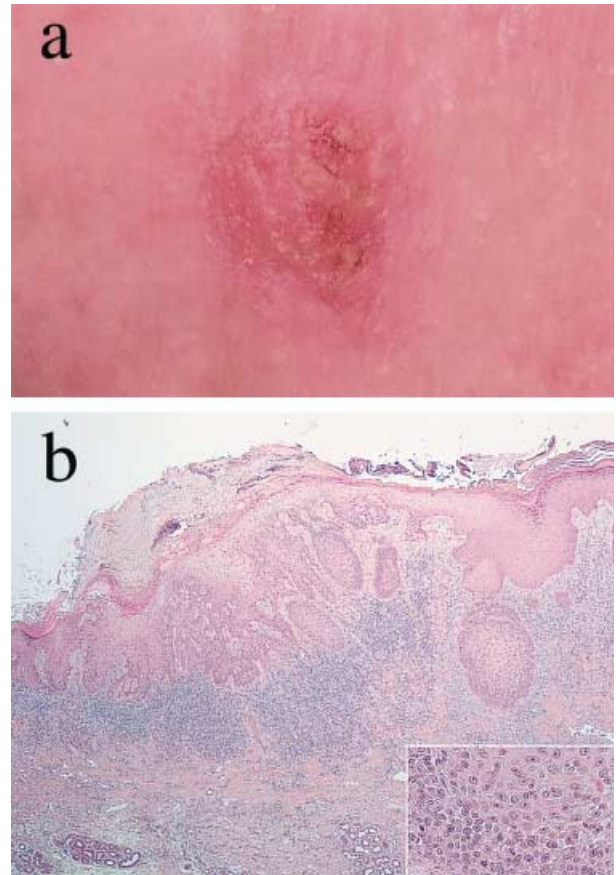
Physical examination at 42 years of age revealed generalized erythema with slight pityriatic scales over almost his entire body (Fig. 1). Mild ectropion was observed. There were severe hyperkeratoses and fissures on the palms and soles, and nail deformity was present on all the fingers and toes. There were no bullous or erosive lesions. Ichthyosis linearis circumflexa, the characteristic clinical features of Netherton syndrome, were not observed. His hair was sparse, but hair shafts did not show trichorrhexis invaginata. A skin biopsy taken from the left shoulder revealed parakeratotic hyperkeratosis with acanthosis. No granular degeneration was



**Figure 1.** Clinical phenotype of NBCIE. The patient showed mild ectropion (a), and erythroderma over the entire body: (b) trunk. The soles exhibited severe hyperkeratosis (c). Hyperkeratosis and erythema with a shiny appearance were seen in the dorsa of left hand (d).

observed. Immunofluorescent staining with B.C1 antibody for TGase 1 showed normal expression of TGase 1 molecule in the patient's epidermis. *In situ* TGase activity assay, performed as previously described,<sup>5</sup> revealed normal enzymatic activity. Electron microscopy did not show any obvious abnormality in keratin filament, lamellar granule, or cornified cell envelope in the patient's epidermis.

He first noticed a hyperkeratotic nodule on his neck at the age of 41 years, which gradually increased in size. When he was 44 years old, a partly verrucous, reddish nodule with crust, about 1 cm in diameter, was present on the left side of his neck (Fig. 2a). The cervical lymph node was not palpable. The nodule was biopsied excisionally with a margin of 1 cm of normal surrounding skin. Histopathologically, there was a proliferative lesion in the epidermis with hyperkeratosis and acanthosis (Fig. 2b). Severe parakeratosis was present in part of the lesion. The tumour invaded irregularly into the dermis, and the basement membrane became obscured in some parts. The tumour cell nuclei were atypical and abundant mitotic figures were present in the tumour nests. Dilated vessels and thick collagen bundles in the dermis suggested scar formation beneath the tumour.



**Figure 2.** Clinical and histopathological features of squamous cell carcinoma on the neck. (a) Hyperkeratotic nodule, approximately 1 cm in diameter, was present on the left side of the neck. (b) Histopathologically, the tumour was invading irregularly into the dermis. The tumour cells had atypical nuclei and some were dyskeratotic. Abundant mitotic figures were observed (inset). Beneath the tumour, a band-like inflammatory cell infiltration and fibrosis were present (haematoxylin and eosin; original magnification  $\times 20$ , inset  $\times 100$ ).

Histopathologically, the surgical margin of the resected nodule was free of the tumour. From these clinical and histopathological observations, the tumour was diagnosed as SCC that presented in a patient with NBCIE. Recurrence of the tumour has not been observed for 3 months after the operation.

As far as we aware, this is the first report of SCC that developed in a NBCIE patient with detailed phenotypic information. The neck is a commonly involved site for SCC because of the high sun exposure and we cannot exclude the possibility of a chance occurrence of SCC in this NBCIE patient. However, the onset of cutaneous SCC at 44 years of age seems to be earlier than normal, especially among the Japanese population.

Amsellem *et al.*<sup>6</sup> demonstrated a higher proliferation rate in keratinocytes in cultures from NBCIE patients by counting

PCNA-positive cells. The increased cell mitoses and consequent high susceptibility to ultraviolet damage might have contributed to skin carcinogenesis in the present case. In addition, there was scar formation in the dermis beneath the tumour. Skin carcinogenesis associated with cutaneous scar is well known, and scarring from chronic inflammation might play a role in the pathogenesis of SCC in our case.

This patient has been treated with systemic etretinate for about 20 years to manage the hyperkeratotic NBCIE lesions. The chemopreventive effect of retinoids for certain cancers is well known, and clinical trials of chemoprevention by retinoids have been performed, which showed positive results for high risk groups of skin cancer, such as patients with xeroderma pigmentosum, basal cell naevus syndrome and patients who received immunosuppressive therapy after organ transplantation.<sup>7-10</sup> Our case developed SCC in spite of etretinate therapy. In previous reports of etretinate chemoprevention, systemic etretinate of 50 mg day<sup>-1</sup> was successful in tumour prevention for organ transplant recipients<sup>9</sup> and etretinate treatment, 1 mg kg<sup>-1</sup> body weight daily was effective for a patient with basal cell naevus syndrome.<sup>10</sup> DiGiovanna<sup>7</sup> recommended 0.25 mg kg<sup>-1</sup> body weight daily as an initial dose of etretinate. The present patient had been taking 10 mg (approximately 0.2 mg kg<sup>-1</sup> body weight) of etretinate daily. The dose of etretinate was effective for the hyperkeratotic lesions of NBCIE, but it would appear to be insufficient for the prevention of carcinogenesis.

In conclusion, during the long-standing follow-up of patients with NBCIE, careful attention should be paid to the occurrence of skin cancer, even if the patients are receiving retinoid therapy.

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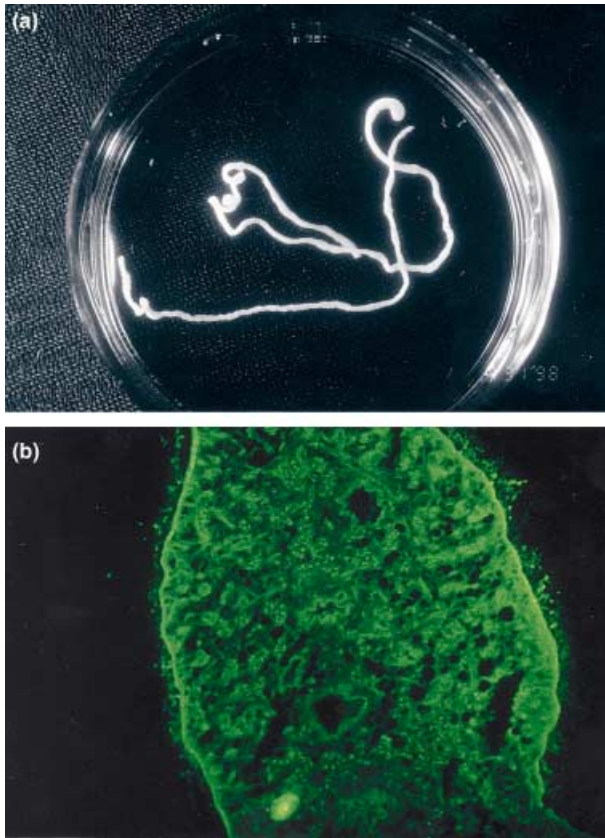
## A case of subcutaneous sparganosis: therapeutic assessment by an indirect immunofluorescence antibody titration using sections of the worm body obtained from the patient

SIR, Sparganosis is a tissue infection caused by plerocercoid larvae or spargana of a species of pseudophyllidean tapeworm of the genus *Spirometra*. The infection is common throughout Asia, especially in Japan where more than 470 cases have been reported. The principle therapy for sparganosis is surgical removal, but sometimes two or more tapeworms may infect the same host. Remaining tapeworms may migrate to other organs, and cause severe systemic complications. We assessed response to surgical removal by measuring antibody titres in serial serum samples with indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). Importantly, we utilized frozen sections of the tapeworm from the patient as the antigen for IIF. The IIF serum titres decreased continuously and the results corresponded to those of ELISA.

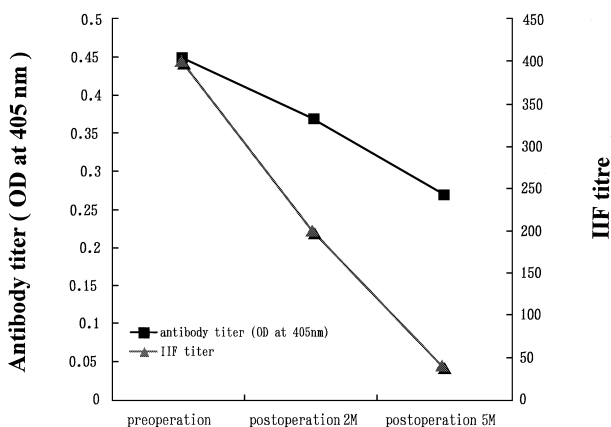
A 59-year-old-woman developed a solitary, nontender, erythematous induration measuring 25 × 12 mm on the left flank. The lesion migrated from the centre of the lumbar region during the course of 3 months. She did not eat raw meat or drink untreated water. A biopsy was carried out under the diagnosis of creeping disease. After incision a milky-white tapeworm was observed moving in the subcutaneous tissue and was removed. The tapeworm measured 10 cm in length and 0.2 cm in width and was smooth-surfaced with a slender ribbon-like shape (Fig. 1a). It was identified as the plerocercoid of *S. erinacei-europaei*.

As the antigen for IIF, the surgically obtained plerocercoid was dissected, mounted in TISSU MOUNT® (Shiraimatu-kiki, Osaka, Japan), and 4-µm frozen sections were prepared. The preoperative serum reacted up to a 400-fold dilution. One and a half months after the operation the serum titre was detected at a 200-fold dilution. Then, after 4 months, the serum reacted up to a 40-fold dilution (Fig. 1b). We also conducted ELISA with an antigen prepared from an extract of the whole worm body of spargana collected from a snake. The serum titre also decreased after the operation (Fig. 2).

Adult *Spirometra* spp. parasitize the gut of canines and felines. Eggs passed into water develop into proceroid larvae in copepod hosts of the genera *Diaptomus* and *Cyclops*. These



**Figure 1.** (a) The tapeworm measuring 10 cm in length and 0.2 cm in width was smooth-surfaced with a slender ribbon-like shape. (b) Antibody binding sites of the sparganum were on the body wall (indirect immunofluorescence with serum at 40-fold dilution; original magnification  $\times 40$ ).



**Figure 2.** The serum titre of enzyme-linked immunosorbent assay (900-fold dilution) and indirect immunofluorescence (IIF). OD, optical density; M, months.

are eaten by frogs, lizards, snakes, birds and some mammals, including mice and monkeys, in which the plerocercoid larvae develop in muscle sheaths. Humans are infected either by the application of raw meat to the skin or eyes, usually as a poultice of Asian medicine, or through eating uncooked meat or drinking water containing infected copepods.<sup>1</sup> However, as in our patient, in more than half of reported cases the cause of infection could not be defined.<sup>2</sup>

Sparganosis commonly affects subcutaneous tissue, especially in the lower abdomen. Extracutaneous lesions are found in the orbita, brain, respiratory organs and urinary tract. In such visceral involvement the result may occasionally be fatal. Although many cases were caused by a single plerocercoid, multiple infections have also been reported. The largest number of worms found in a single patient was 12.<sup>3</sup>

An immunological diagnosis for this disease was demonstrated by Okabe and Murase,<sup>4</sup> using the immunoprecipitation and intracutaneous reaction. Ishii<sup>5</sup> introduced the IIF method, using snake sparganum, and Mukai *et al.*<sup>6</sup> utilized the complement fixation reaction or the haemagglutination test. ELISA was reported as a useful technique for diagnosis and confirming that the treatment was successful.

If the serum titre decreases 3 months after the operation, the patient is considered free from the parasite.<sup>7</sup> In our case, the decreasing serum titre after surgery was parallel in IIF and ELISA. Therefore, IIF was found to be useful in assessing the absence of tapeworm after the operation. It is familiar for most dermatologists to conduct IIF in their own laboratories. The frozen section can be preserved for a long time. Ishii previously conducted IIF on five sera of human sparganosis patients.<sup>5</sup> He used sparganum collected from a snake, *Elaphe quadrigata*, for the antigen in IIF. However, it is almost impossible for dermatologists to obtain snake sparganum. We emphasize that we should keep the frozen specimen of the surgically obtained tapeworm for further IIF follow-up.

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### Audit of basal cell carcinoma: registration practice

SIR, Basal cell carcinomas (BCCs) are the commonest form of skin cancer, with increasing incidence in the U.K.<sup>1</sup> They are associated with significant morbidity and their cost of treatment is an increasing burden to the health service, yet accurate information on their incidence is not available.<sup>2</sup> For cost and volume reasons BCCs are not recorded by all cancer registries. The Northern Ireland Cancer Registry (NICR), however, collects data on skin cancers and reports BCCs as accounting for almost 18% of all cancers diagnosed.<sup>3</sup>

The NICR follows the European Network of Cancer Registries (ENCR) guidelines that only the first occurrence of non-melanoma skin cancers is routinely reported.<sup>4</sup> Accurate and up-to-date records on BCCs are necessary for quantification of changes in their incidence, to allow for research and planning of services. There was concern that BCCs were being under-reported due to the ENCR guidelines. An audit was therefore undertaken to determine the accuracy and completeness of the records held and reported by the NICR for BCCs. The standard target was set at 100% for accuracy and completeness of records. It was also felt that data should be held regarding the size, location and morphology of the tumour, as well as the sex and age of the patients.

The NICR obtains data electronically from several sources. For BCCs a significant amount of the information is received from pathology laboratories. Most BCCs excised are sent for histological analysis. The Royal Victoria Hospital pathology laboratory provides a service for a large catchment area including other hospitals and general practitioners. It processes approximately 40% of all the skin tumours reported in Northern Ireland. We obtained a record from this laboratory of biopsies for 6 months in 1999 with a diagnosis of BCC. This list was electronically and manually cross-checked with the NICR records for the same period. The number of BCCs registered and the details documented were analysed.

Four hundred and fifty-five 'BCC' biopsies were identified, occurring in 403 patients. It was clear that some patients had had more than one biopsy. The medical notes were studied and on further analysis it was determined that the 455 biopsies corresponded to 407 BCCs. All were recorded by the registry, but due to application of ENCR guidelines, only 270 (66%; 95% confidence interval, CI 62–71%) of these were reported by the NICR. One lesion was registered as Bowen's disease: this was probably an error in coding. Twelve lesions

were registered as malignant neoplasms nonspecified, as this was the information received from pathology. Sex and date of birth were recorded for all patients. No details on size or location were recorded for the tumours.

This audit confirms that the full incidence of BCCs is not reflected by the numbers reported by the NICR, which underestimated their true extent by 33% (95% CI 29–38%). It is essential that both recurrences and multiple BCCs be considered when estimating the true burden of this tumour. In addition, many of the details about BCCs, which may influence outcome, are not being recorded.

Following this audit the dermatology department is piloting the use of standard request forms for skin tumours which require information on site, location, size, history, suspected diagnosis, incisional or excisional biopsy, margins, origination and previous numbers of biopsies. A proforma for reporting of the tumours by the pathology department is also being developed. It is hoped that with an increase in the clinical information received, along with the standardization of the pathology details, additional high-quality information will be captured by the NICR, which will improve the quality of data recorded for each tumour.

In conclusion, this audit has identified that BCC reporting underestimates the true extent of the disease. Through close liaison between the departments of Dermatology, Pathology and the Cancer Registry we have modified the system to address some of the issues raised by this audit. We hope that the changes to the system for recording tumour data will result in more accurate and complete information on BCCs that fully reflects the burden of skin cancer in our community.

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### Late (> 10 years) recurrence of melanoma: the Scottish experience

SIR, Recurrences of melanoma 10 years or more after diagnosis have been reported in 0.93–6.7% of patients.<sup>1–8</sup> We have established, using the Scottish Melanoma Group (SMG) database, the incidence of late recurrence in a defined population and have tried to identify particular patient or tumour characteristics associated with higher risk of late recurrence.

Ten years or more follow-up have been completed by 3822 SMG-registered patients. Twenty-five (12 men, 13 women) of 3822 (0.65%) have had first recurrence 10 years or more after primary surgery. The mean age at primary diagnosis was 57.6 years (men) and 50.5 years (women). The most common primary lesion site was the trunk in men (five of 12, 41.7%) and the leg in women (seven of 13, 53.8%). In comparison, 24.9% of men on the complete database had a primary lesion on the trunk and 42.3% of women had a primary lesion on the leg.

The most common tumour type in those with late recurrence and the entire group was superficial spreading malignant melanoma (52% and 54%, respectively). The relative frequencies of nodular malignant melanoma (24% and 21%) and lentigo maligna melanoma (12% and 11%) were also similar.

The median time to recurrence in the 25 patients with late recurrence was 11 years (range 10–19), with no difference between men and women. For primary lesions of 0.1–1 mm thickness, the median time to relapse was 11 years (range 10–15), for those 1.01–3 mm, 12 years (range 10–19) and for those >3.01 mm, 11 years (range 10–13). The site of recurrence was local lymph nodes in three, viscera in six, local cutaneous in four and distant cutaneous in three. In eight patients, recurrence was noted at several sites simultaneously. In one patient the pattern of recurrence was unclear. Truncal primaries most commonly metastasized to the viscera (four of five), with only one of five recurring in regional lymph nodes.

Tumour thickness in the late-recurrence patients ranged from 0.2 to 5.8 mm, with a mean value of 2.37 mm in men and 2.07 mm in women. The distribution of Breslow thickness was similar in the database and late-recurrence patients. Thin melanomas (under 1 mm) were equally common in the late-recurrence and other database patients, at 36% and 41%, respectively. This was also the case for intermediate-thickness lesions (1.01–3 mm), 36% and 32%, respectively, and lesions >3.01 mm in thickness, 28% and 27%, respectively.

Survival depended on the site of recurrence. Thirteen patients have died of melanoma. The median survival for those with visceral metastases was 6 months (range 5–24) compared with 49.5 months (range 12–73) for those with other metastatic patterns.

The reported incidence of late melanoma recurrence varies widely in the literature, from 0.93%<sup>3</sup> to 6.7%.<sup>1</sup> The incidence of late recurrence in our Scottish population (0.65%) is lower

than previously reported. The incidence of 0.93% reported by Callaway and Briggs is the closest to the findings of the present study.<sup>3</sup> The disparate results may be accounted for, in part, by inclusion/exclusion criteria and by completeness of follow-up. Ocular melanoma has been included in some analyses<sup>4</sup> and behaves differently to cutaneous melanoma. All of our patients have cutaneous melanoma, and our data pertain to a whole population, which should give a more accurate reflection of incidence of late recurrence. Furthermore, only patients with a full 10 years or more of follow-up data have been included in our study.

There were equal numbers of men and women affected in our series. This has been the case in some previous reports,<sup>2,5</sup> but is at variance with the findings of others,<sup>1,6</sup> who noted a female preponderance.

The tumours in our patients were thicker (mean 2.2 mm) than in previous reports, where thickness ranged from 1.4<sup>5</sup> to 2.0 mm.<sup>2</sup> Day *et al.* reported that death from melanoma after 5 years occurred exclusively in lesions of Breslow thickness 1.7–3.64 mm.<sup>7</sup> Clearly this is not the case in our patients, nor has it been the experience of other authors.<sup>1,2,4,5</sup> There was no clear relationship in our series between thickness of the primary tumour and time to recurrence.

Cascinelli *et al.*<sup>8</sup> have suggested that when the interval between primary surgery and first recurrence of melanoma exceeds 5 years, the tumours are more likely to be located at sites other than the back, arms, neck and scalp (BANS). Nineteen of 25 (76%) of our patients had primary melanomas at nonBANS sites. Shaw *et al.*<sup>2</sup> found that men with late first recurrence had lesions predominantly on axial sites and women on the extremities. Although the latter held true for our patients, the men in our study had roughly equal numbers of extremity, facial and axial lesions (five, three and four, respectively). Eight of 25 patients experienced recurrence at several sites simultaneously. This appears unusual, but as the number of patients in our study is small, the significance of such an observation is unclear.

The incidence of late recurrence is low. An ageing population, an increasing incidence of melanoma in certain sections of the population and a relatively young age at diagnosis means that the burden of long-term follow-up of patients with cutaneous malignant melanoma is considerable. At the time of presentation with late recurrences, most patients have been discharged from hospital follow-up or are only attending annually. Given that the rate of late recurrences is very low, prolonging hospital follow-up cannot be justified for the majority of patients. Recurrences are therefore likely first to be identified by the patient, who should know what to look for and what action to take. Late locoregional recurrences are potentially curable and therefore lifelong monthly self-examination of the skin, local and regional nodal basin is to be recommended. Unfortunately, it was not possible to identify particular host or tumour characteristics that permit prediction of those at risk of late recurrence of melanoma.

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## Dermatology Life Quality Index score in vitiligo and its impact on the treatment outcome

SIR, Vitiligo is an acquired depigmentation disorder of great cosmetic importance affecting 1–4% of the world's population. The disease has a major impact on quality of life of patients, many of whom feel stigmatized by their condition. Porter *et al.* studied the effect of vitiligo on sexual relationships and found that embarrassment during sexual relationships was especially frequent for men with vitiligo.<sup>1</sup> Salzer and Schallreuter<sup>2</sup> reported that 75% found their disfigurement moderately or severely intolerable. Weiss *et al.*<sup>3</sup> compared the difficulties faced by patients with vitiligo with those with leprosy in India. There may be a relationship between stress and the development of vitiligo. Al-Abadie *et al.*<sup>4</sup> indicated that psychological stress increases levels of neuroendocrine hormones, affects the immune system and alters the level of neuropeptides, which may be the initial steps in pathogenesis of vitiligo. The purpose of this study was to assess the nature and extent of the social and psychological difficulties associated with vitiligo and their impact on treatment outcome by using the Dermatology Life Quality Index (DLQI).

One hundred and fifty patients with vitiligo vulgaris involving more than 10% body surface area attending the pigmentedary clinic of the Department of Dermatology, Postgraduate Institute of Medical Education and Research,

Chandigarh, India were enrolled in this study. They were introduced to the subject of this study and informed about the personal nature of the questionnaire, and all those who gave consent were given the DLQI questionnaire to complete. Before starting therapy, patients were evaluated clinically to record the duration and progression of the disease, the sites of lesions, and the extent of cutaneous involvement. These patients were treated as per protocol of our pigmentedary clinic. Two parameters, repigmentation and arrest of progression of disease activity, were used to evaluate the response to treatment. The treatment was considered to be successful if a patient with active disease: (i) had no new lesions; (ii) had no increase in the size of the existing lesions; and (iii) had more than 25% repigmentation at the end of 1 year. The treatment was considered to be a failure: (i) if a patient with active disease continued to have new lesions; or (ii) if the existing lesions continued to increase in size; or (iii) there was less than 25% (overall) repigmentation at the end of 1 year of treatment. Responses on the DLQI were scored according to the guidelines of Finlay and Khan.<sup>5</sup>

One hundred and fifty patients completed the questionnaire. Their basic data are given in Table 1. Scores on the DLQI ranged from 2 to 21 (mean  $\pm$  SD 10.67  $\pm$  4.56). There was no statistically significant difference between the DLQI scores of the male and female patients. There were statistically significant relationships between DLQI scores and age ( $P < 0.001$ ), and between DLQI scores and disease duration ( $P < 0.05$ ), but not between DLQI scores and other variables such as extent of disease.

At the end of the treatment period, 141 patients could be evaluated. The treatment outcome was considered to be successful in 91 patients and a failure in the remaining 50, based on the criteria mentioned above. The mean DLQI score was 7.06 in patients with a successful outcome, whereas it was 13.12 for patients with treatment failure. There was a statistically highly significant difference ( $P < 0.0001$ , *t*-test) between mean DLQI scores of these two groups.

**Table 1.** Basic data of patients in this study

	Total patients ( <i>n</i> = 150)
Age, mean (range), years	33.6 (18–63)
Sex, M/F	67/83
Duration of disease	
< 1 year	27
1–3 years	76
> 3 years	47
Treatment modalities	
PUVA	12
PUVAsol	85
OMP	18
PUVAsol and OMP	7
PUVAsol and levamisole	28

PUVA, psoralen plus ultraviolet A therapy; OMP, oral mini pulse (betamethasone).

This study provides information concerning the DLQI and its impact on treatment outcome in vitiligo sufferers. The mean DLQI score in our study (10.67) is higher than that obtained by Finlay and Khan<sup>5</sup> (mean 7.3) and Kent and Al-Abadie<sup>6</sup> (4.82). There was no relationship of DLQI score with gender, which is consistent with the earlier studies. Our study clearly demonstrated that patients with high DLQI scores responded less favourably to a given therapeutic modality. These results suggest that additional psychological approaches may be particularly helpful in these patients.

In a preliminary study by Papadopoulos *et al.*,<sup>7</sup> it was shown that counselling can help to improve the body image, self-esteem and quality of life of patients with vitiligo as well as having a positive effect on course of the disease. There is evidence that social and psychological well-being increase when patients with facial disfigurement are helped to develop social skills and to confront their difficulties. In a disease such as vitiligo, which is not only difficult to treat but is likely to progress, it is important to recognize and deal with the psychological component of this distressing condition not only to improve the appearance-related stress-handling capability of the patient but also to obtain a better treatment response. Training in assertiveness, relaxation skills and help in building self-confidence would have substantial effects on DLQI score as well as treatment outcome. The results of this study have implications in terms of our understanding of the role of the mental state and its impact on treatment outcome in vitiligo.

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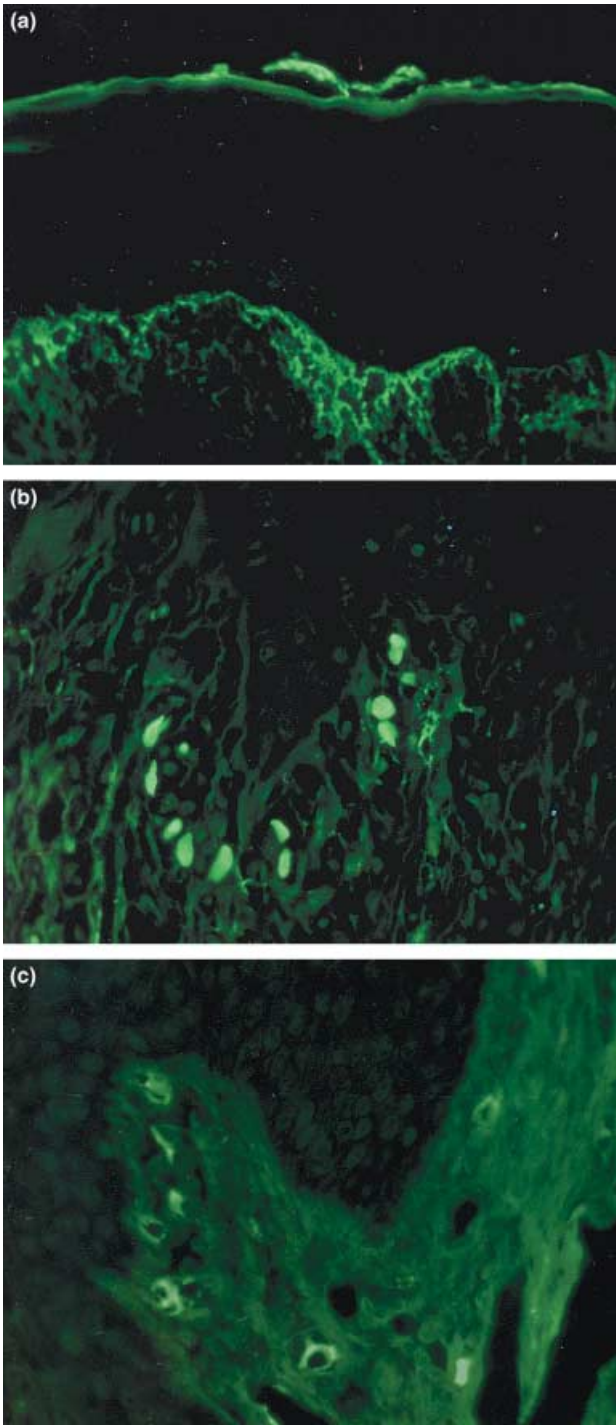
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#### Oral lichen planus: diagnostic immunofluorescence testing on routine histological material

SIR, Direct immunofluorescence testing on lesional biopsies is a valuable tool to establish the diagnosis of oral lichen planus (OLP) and to differentiate the condition from other immunologically mediated diseases of the oral mucosa, such as pemphigoid, pemphigus vulgaris and lupus erythematosus. Shaggy deposition of fibrinogen along the basement membrane zone and/or globoid or cytooid-like bodies with positive IgM labelling have been shown to represent typical and diagnostic features of OLP, in particular when used in conjunction with routine histology.<sup>1–3</sup> However, correlative and, most importantly, retrospective evaluations on routine histological material do not seem possible, as specific and reliable immunolabelling is thought to require fresh-frozen biopsy specimens.<sup>4,5</sup> We present a simple and effective technique for diagnostic immunofluorescence testing on archival histological material from oral biopsies.

The study was performed on 30 diagnostic biopsies taken from the buccal or gingival mucosa of 27 patients (20 women, seven men; mean age 54 years) suspected to suffer from OLP. All biopsies had been fixed in formaldehyde and embedded in paraffin using conventional techniques. For immunofluorescence testing, dewaxed and rehydrated histological sections were treated with 0.1% (w/v) pronase E (Sigma, St Louis, MO, U.S.A.) in 0.1 mol L<sup>-1</sup> Tris-buffered saline (TBS) for 30 min at 37 °C. After washing in TBS, the sections were incubated with fluorescein isothiocyanate (FITC)-conjugated polyclonal rabbit antibodies against IgG, IgA, IgM, complement C3 and fibrinogen (all from Dako, Hamburg, Germany) for 30 min at room temperature. The specificity of staining was checked by incubating the sections with FITC-conjugated normal rabbit serum. The labelled sections were washed in TBS, mounted in Immunomount-Shandon, coverslipped and examined with a conventional Zeiss light microscope equipped with a 200-W mercury arc lamp.

Immunofluorescence examination showed excellent preservation of tissue morphology, and negligible background staining, nonspecific fluorescence and tissue autofluorescence. No positive immunofluorescence staining was observed in normal oral mucosa biopsies ( $n = 5$ ) used as negative controls. The positive controls from oral pemphigus vulgaris ( $n = 3$ ) and mucous membrane pemphigoid ( $n = 3$ ) were characterized by typical and distinct staining of the epithelial intercellular spaces and basement membrane zone, respectively. The typical immunofluorescence staining patterns of OLP were found in 17 of the 30 histological biopsies.



**Figure 1.** Immunofluorescence staining patterns. (a) Shaggy deposition of fibrinogen at the basement membrane zone (original magnification  $\times 100$ ). (b) IgM-positive cytooid-like bodies at the basement membrane zone and papillary submucosa (original magnification  $\times 400$ ). (c) Fibrinogen deposition at small blood vessels of the papillary submucosa (original magnification  $\times 400$ ).

There were 13 biopsies with shaggy deposition of fibrinogen along the basement membrane zone (Fig. 1a), three biopsies with both shaggy fibrinogen deposition and IgM- and less often IgG- and IgA-positive cytooid-like bodies in the lower epithelial and papillary submucosa, and one biopsy with IgM-positive cytooid-like bodies but no shaggy fibrinogen deposition (Fig. 1b). Other staining patterns observed were each present in only one biopsy, except for fibrinogen labelling of the small blood vessels in seven specimens (Fig. 1c).

To evaluate the sensitivity and specificity of this technique, the immunolabelling patterns were compared with the histological features of the biopsies. Histological diagnosis and classification of OLP were made according to the World Health Organization criteria modified by McCartan and Lamey.<sup>6,7</sup> This comparison (Table 1) revealed only a few instances of false-negative immunolabelling in the biopsies with histologically evident OLP, and only one of false-positive labelling in the biopsies showing no histological support for OLP. In six of the nine biopsies with histological alterations that were only compatible with OLP, the diagnosis was established by a typical immunofluorescence staining pattern. Remarkably, one of these specimens contained a squamous cell carcinoma in close apposition to the inflammatory alterations. The fibrinogen labelling of the blood vessels showed no correlation with the histological classification, but it was always related to vascular inflammatory infiltrates.

The main problem in immunofluorescence testing on histological material is the formalin-induced cross-linking and antigenic masking of the deposition of interest.<sup>4,5</sup> The technique introduced in this study resulted in effective unmasking of antigen sites, with distinct, intense and specific immunolabelling and negligible background staining of the histological sections. The archival biopsy material with histologically proven OLP showed the same diagnostic staining patterns as observed in fresh-frozen biopsies.<sup>1-3</sup> The sensitivity and specificity of these staining patterns, which were calculated from the histological diagnoses made on the same specimens, were superior to those after antigen retrieval by trypsin digestion,<sup>8</sup> and seemed even to be comparable with fresh-frozen tissue.<sup>3</sup> The latter estimation must, however, be verified by comparative analyses on formalin-fixed, paraffin-embedded and fresh-frozen biopsy material, not available in this retrospective study. Nevertheless, the diagnostic significance of our technique has already been proven by the establishment by immunofluorescence of OLP in several biopsies showing, on histological examination, inflammatory alterations that were compatible with, but not evident for the diagnosis. The detection of a squamous cell carcinoma in one of these biopsies suggests malignant transformation of the OLP, which in particular occurs in long-standing atrophic and erosive disease.<sup>9</sup> Taken together, immunofluorescence testing on pronase-treated histological sections is a valuable diagnostic tool that

**Table 1.** Comparison of the histological and immunofluorescence findings

Histopathology classification	n	Immunofluorescence testing		
		OLP patterns <sup>a</sup>	Other patterns	Negative
Evident OLP	13	10	3	0
Compatible with OLP	9	6	2	1
No support for OLP	8	1	5	2

OLP, oral lichen planus. <sup>a</sup>Shaggy deposition of fibrinogen along the basement membrane zone and/or IgM-positive cytooid-like bodies.

improves the often controversial histopathological assessment of OLP.<sup>10</sup>

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### Severe pruritus in a haemodialysed patient: dramatic improvement with granisetron

SIR, Pruritus is a common unpleasant symptom in patients undergoing dialysis. Uraemic pruritus can be resistant to conventional antipruritic therapy and can affect the patient's quality of life. We report a haemodialysed patient with resistant pruritus who showed a dramatic improvement after treatment with granisetron.

A 51-year-old man on haemodialysis since 1982 presented with a 1-year history of pruritus. He did not improve with any major antipruritic therapy (hydroxyzine, antihistamines class I and II). He was depressed because he had been unable to sleep for the previous year due to the distressing pruritus. His medical history included hyperparathyroidism and hepatitis B and C virus infection.

Examination showed global excoriated and necrotic areas, mainly over the thorax (Fig. 1a). He was started on granisetron 1 mg daily. Within a few hours of the first dose the patient reported a dramatic relief of the pruritic discomfort, enabling him to sleep. Pruritus, scratching and global excoriation gradually improved (Fig. 1b). Treatment was continued for 3 weeks. No side-effects were observed. The patient remained free of symptoms 3 months after stopping this drug.

Granisetron and ondansetron belong to the 5-hydroxytryptamine type 3 (5HT<sub>3</sub>) receptor antagonists. These drugs are selective inhibitors of the 5HT<sub>3</sub> receptor and have a potent antiserotonin effect. The anti-5HT<sub>3</sub> drugs are usually employed to relieve chemotherapy-induced emesis.<sup>1</sup> Serotonin could play a key role in the generation of this symptom.<sup>2</sup> Additionally, serotonin and histamine have been reported as possible mediators of uraemic pruritus. Ondansetron has been reported to improve pruritus in dialysis patients<sup>2</sup> and in palmoplantar pruritus resistant to other therapies.<sup>3</sup> These drugs have occasionally been used for cholestatic pruritus.<sup>4</sup>

Our case indicates that granisetron could be an effective, safe and well-tolerated drug to treat uraemic pruritus in

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**Figure 1.** (a) Excoriated and necrotic areas on the thorax in a dialysed patient. (b) Improvement of the lesions after treatment with granisetron.

dialysed patients. More studies would be needed to prove the effectiveness of this drug for uraemic pruritus.

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#### ***Borrelia afzelii* evidenced by polymerase chain reaction in a biopsy of nipple lymphocytoma**

SIR, Typically located in the ear lobe, nipple areola, nose and scrotum, *Borrelia* lymphocytoma is not rare but is often misdiagnosed.

A 57-year-old man had had an infiltration of the left areola and nipple for 3 months. The infiltrated area strictly corresponded to anatomical limits; tissues were firm, elastic and homogeneous. The colour was dark red. The patient reported a local painful hyperaesthesia. Two months before the first signs appeared, in the summer, he had noticed an erythematous macule in the same area. After a few weeks of slow progression, this plaque had a diameter of almost 15 cm, before resolving spontaneously. Two mammograms showed a thickening of the areolar plaque. The tumour cell markers CA125, carcinoembryonic antigen and CA19-9 were negative. Fine needle biopsy suggested an inflammatory reaction, without atypical or malignant cells. Symptoms were suggestive of a pseudolymphoma. The patient had not previously noticed any tick bite. *Borrelia* serodiagnosis by enzyme-linked immunosorbent assay (IgM and IgG) was negative. Skin

biopsy of the areola showed a dense perivascular and interstitial lymphohistiocytic infiltrate, with nonspecific fibrous changes of connective tissue. A diagnosis of *Borrelia* lymphocytoma was made by polymerase chain reaction (PCR) performed with a cryopreserved skin specimen, and was highly positive for *B. afzelii*. Doxycycline 200 mg daily was given for 4 weeks. At the end of treatment, the appearance of the breast was normal.

DNA was extracted from fresh frozen tissue using a commercially available DNeasy kit (Qiagen, Westburg, the Netherlands), following the manufacturer's instructions. The extracted DNA was used as a template in the PCR assays. Purified DNA from the cultured spirochaete *B. burgdorferi sensu strictu* B31 was used as a positive control. This was a kind gift from E. Godfroid (Free University of Brussels, Nivelles, Belgium). The SL primers (5'-AATAGGTCTAATATTAGCCTT AATAGC-3', 5'-CTAGTGTCTTTGCCATCTTCTTTGAAAA-3') were used to amplify a 308-bp fragment of the *ospA* gene by PCR.<sup>1</sup> The reaction mixture consisted of deoxynucleoside triphosphates dATP, dGTP, dCTP and dTTP (200 µmol L<sup>-1</sup>), SL primers (0.2 pmol each), AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, CA, U.S.A.), heat labile uracil DNA glycosylase (Roche Molecular Biochemicals, Mannheim, Germany) and 10 µL of extracted DNA. PCR amplification cycles were as follows: one cycle of 10 min at 20 °C; one cycle of 10 min at 94 °C; 50 cycles of 1 min at 94 °C, 1 min at 62 °C, 1 min at 72 °C; one cycle of 10 min at 72 °C. Amplicons were visualized on a 2% agarose gel stained with ethidium bromide. Southern blotting and non-radioactive hybridization were performed to confirm the specificity of the PCR amplification product. Amplicons were transferred on to a positively charged nylon membrane (Porablot NY, Filter Service). Hybridization with digoxigenin-labelled probe 5'-AAGTTCCTTTAAGCTCAAGCTTGCTACT GTT-3' adapted from Mansy *et al.*<sup>2</sup> was performed with a commercial Dig Nucleic Acid detection kit according to the manufacturer's instructions (Roche Molecular Biochemicals). The 308-bp *ospA* product was purified from agarose gel by the QIAquick Gel Extraction kit (Qiagen). Analysis of the sequence was performed with an automatic DNA sequencer (Perkin-Elmer, Applied Biosystems) using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction kit. The sequence was compared with the sequence data available in databases using BLAST. The *ospA* sequence exhibited 97%, 89% and 90% similarity to *ospA* sequences of *B. burgdorferi afzelii*, *B. burgdorferi sensu strictu* and *B. burgdorferi garinii* strains, respectively.

Lymphocytoma (Bafverstedt) is a late manifestation of skin borreliosis, which is mostly observed in Europe.<sup>3</sup> Diagnosis is essentially clinical. The causal tick bite is frequently not noticed. Serological detection has poor specificity and sensitivity, particularly during the first weeks of infection.<sup>4</sup> Skin biopsy is not discriminant: the dermal infiltrate is dense, with small lymphocytes and grouped lymphoblasts resembling germinal centres; this aspect may suggest a B-cell lymphoma. In practice, only the direct detection of *Borrelia* constitutes a viable diagnosis method. As culture is difficult, the best

method of diagnosis is PCR performed on a skin biopsy.<sup>5</sup> Very few articles report *Borrelia* species identification from a skin biopsy. In one series of five solitary lymphocytomas, four biopsies were positive for *B. afzelii*;<sup>6</sup> this study was from Slovenia, where *B. afzelii* is the predominant genospecies of *Borrelia*. In another report, two cases were positive for *B. garinii*.<sup>7</sup> In contrast, most American rheumatological and neurological signs of Lyme disease are due to *B. burgdorferi sensu strictu*. As previously suggested, there may be a predilection and a relative specificity of each genospecies for each symptom of borreliosis. In southern Belgium, 23% of 489 *Ixodes ricinus* ticks collected were found to be infected by *Borrelia* sp. (53% *B. burgdorferi garinii*, 38% *B. burgdorferi sensu strictu* and 9% *B. burgdorferi afzelii*, with numerous coinfections).<sup>8</sup>

Many misdiagnoses could be avoided if PCR were systematically performed for subacute areola and nipple tumefaction. Most cases resolve spontaneously within a few months. However, treatment is necessary to avoid tertiary symptoms of borreliosis. Treatment is simple and effective (tetracyclines). Some decades ago, mastectomy was sometimes erroneously performed for lymphocytoma.<sup>9</sup> Today, many expensive and useless examinations as well as much anxiety could still be avoided through better recognition of the disease.

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### Arterial embolization caused by injection of hyaluronic acid (Restylane)

SIR, the report of arterial embolism caused by one of the hyaluronic acid (Restylane) fillers<sup>1</sup> is an important reminder that dermal fillers are not without a variety of safety concerns.<sup>2,3</sup> I have observed a vascular problem in the upper lip that resulted from a delayed Restylane reaction causing venous occlusion with a resulting varix and persistent tissue swelling that has lasted 6 years. The varix was confirmed by skin biopsy, there being no residual detectable hyaluronic acid using appropriate histopathological stains.

In addition, the authors may be interested in our recently published paper on hyaluronic acid dermal filler reactions and skin testing.<sup>2</sup> We have in this paper documented delayed reactions to Hylaform and Restylane in approximately 0.4% of 709 patients. They were seen between 1996 and 1999. It is to be noted that the reaction rate to Restylane has decreased since 1999 when the formulation was changed (Lowe NJ, manuscript in preparation).

The widespread use of dermal fillers by non-medically qualified practitioners is not, in my opinion, in the interest of the public; the letter by Schanz *et al.* highlights a new risk that these agents can cause.

The rapid approval of dermal fillers without adequate safety testing is also not in the interest of the general public and the medical devices agencies should be scrutinizing any new dermal filler in much greater detail than is currently the situation in Europe.<sup>4</sup> Several other fillers have been withdrawn, e.g. Evolution (Europe) and Dermologen (U.S.A.), because of side-effects.

In most patients Restylane, Perlane and Hylaform hyaluronic acid fillers are safe when given by trained physicians. However, those treating physicians need to be familiar with the small potential for adverse reactions and their management.<sup>5</sup>

I thank Dr Schanz and his colleagues for bringing this additional potential risk from dermal fillers to our attention.

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### Arterial embolization caused by injection of hyaluronic acid (Restylane): reply from authors

SIR, We thank Dr Lowe for his kind remarks concerning our case of arterial embolization after injection of hyaluronic acid (Restylane).<sup>1</sup> We fully agree with his advice that dermal fillers should be applied only by trained physicians who also know about the potential risk of arterial embolization. However, it should be pointed out once more that this seems to occur very rarely and our patient was the first reported case with this serious complication after injection of Restylane. More frequent delayed reactions are seen, as documented by Dr Lowe in 0.4% of the patients treated with Hylaform or Restylane.<sup>2</sup>

As an alternative option for correction of glabellar lines, treatment with botulinum toxin should be mentioned here. Several reports show that this agent is effective and safe in the treatment of hyperkinetic facial lines.<sup>3–5</sup> The effects are usually seen 24–72 h after injection. They last from 3 to 6 months,<sup>3</sup> which is comparable to the use of Restylane.

Although botulinum toxin is generally well tolerated, adverse reactions are also documented for this substance. Blitzer *et al.* describe a temporary weakness of adjacent muscles;<sup>3</sup> Goodman even reports temporary eyebrow ptosis.<sup>4</sup>

As in the use of filler substances, these side-effects can be minimized with a thorough understanding of the facial soft-tissue anatomy,<sup>5</sup> so, in our opinion, all these facial aesthetic treatment options should be used only by experienced physicians.

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### Prevalence of hypertension among patients with atopic dermatitis

SIR, Uehara *et al.* recently reported the incidence of hypertension in a Japanese adult population with atopic dermatitis to be 1.1% and 1.6% in men and women, respectively.<sup>1</sup> These figures may be unique to their specific patient demographics rather than representative of all patient populations.

In a recent U.S. study, 89 381 patients with atopic dermatitis and eczema were analysed to determine their annual costs of illness.<sup>2</sup> Patients were identified through submitted claims histories. Within a population of atopic dermatitis patients ( $n = 19\ 664$  identified by ICD-9-CM diagnosis code 691.8) of all ages insured by a public payer, we found the prevalence of essential hypertension (ICD-9-CM diagnosis code 401) to be 5.0% across all patients (3.8% males, 5.8% females). Furthermore, we found that hypertension prevalence ranged from 0.2% in patients within the age range 0–16 years, and went as high as 50.3% in patients over the age of 60 years. The prevalence of hypertension in atopic dermatitis patients over the age of 16 years was 19.8%.

Our research results contrast sharply with data obtained directly from patients in Japan. Differences may be due to patient ethnicity and demographics, sample sizes, and methodologies. Nonetheless, they point to the need for additional research into the comorbidities associated with atopic dermatitis.

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### Prevalence of hypertension among patients with atopic dermatitis: reply from author

SIR, After reading the letter by Abramovits *et al.* I thought that the great disparity between their research results and our data was mainly due to differences in the method of diagnosing atopic dermatitis. In our study,<sup>1</sup> we observed skin symptoms in all patients, and diagnosed their skin disease as atopic dermatitis by using the internationally accepted diagnostic criteria of Hanifin and Rajka.<sup>2</sup> Thus, I believe that our patients were all typical cases of atopic dermatitis.

In the study of Ellis *et al.*<sup>3</sup> patients' skin symptoms were not observed; the diagnosis of atopic dermatitis was made on the basis of health care claims data obtained from different payer populations. It is then evident that their diagnosis lacked accuracy and might have been used too broadly. The diagnostic confusion makes it difficult to compare their research results with our data.

Nevertheless, as information on blood pressure in patients with atopic dermatitis is scant,<sup>1</sup> further studies in different countries are needed to determine the prevalence of hypertension in patients suffering from the disease.

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### The early erosive vesicular stage of lipoid proteinosis: clinical and histopathological features

SIR, Lipoid proteinosis (LP) is a rare autosomal recessively inherited disorder, which is characterized by the deposition of hyaline-like material in the skin, mucous membranes and

other tissues.<sup>1-3</sup> The presenting manifestation of LP is hoarseness due to involvement of the larynx, which remains throughout life.<sup>4</sup> The skin lesions usually appear during the first 2 years of life and occur in two overlapping stages. In the first stage, vesicles, bullae and haemorrhagic crusts appear spontaneously, and resolve with scarring. In the second stage, the skin becomes thickened and yellowish due to the deposits, and waxy papules and plaques develop predominantly on the face, scrotum and axillae.<sup>1-3,5,6</sup> As detail about the evolution and histopathology of early lesions of LP is lacking, we describe the early erosive vesicular lesions in detail both clinically and histologically.

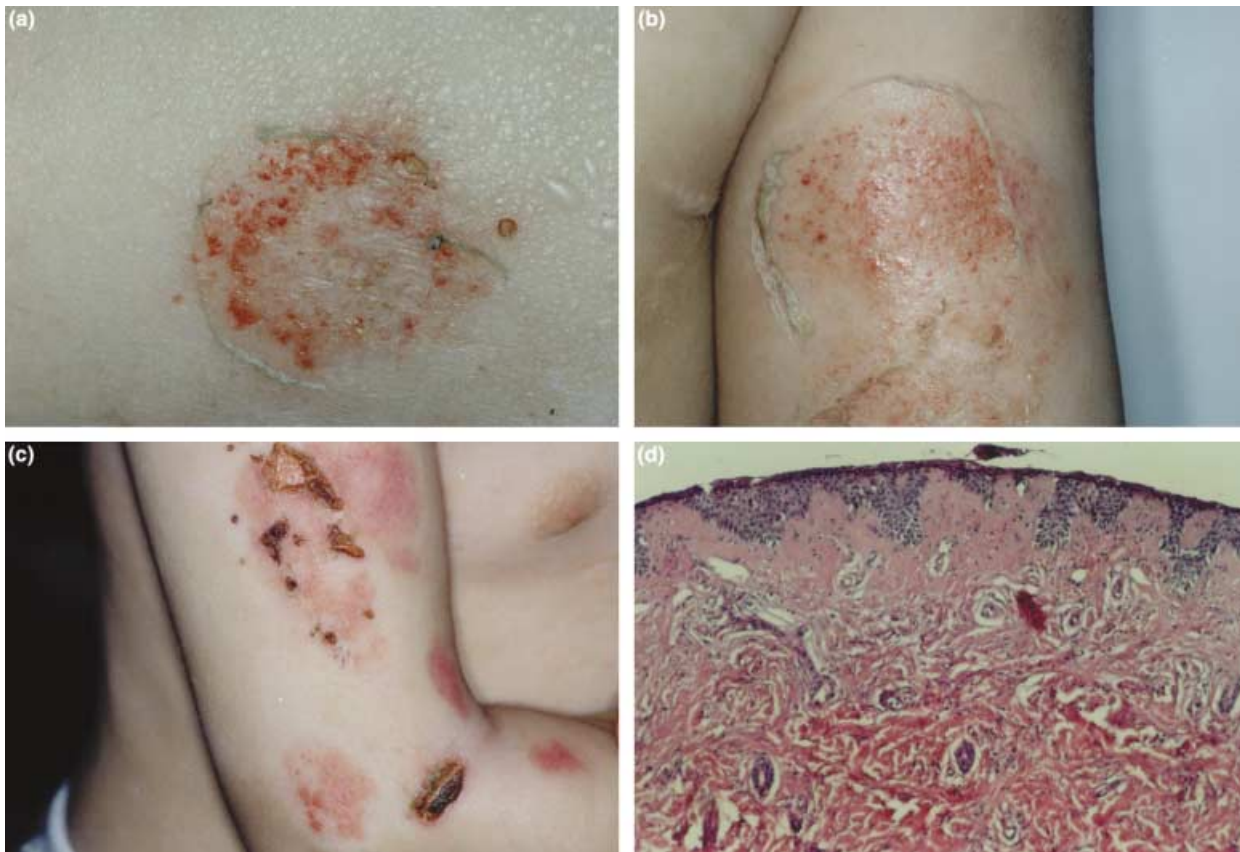
A 4-year-old girl presented with eroded lesions. She had been followed up for 3 years following the diagnosis of LP. In this period of time the disease course showed fluctuations and she had some severe activations, especially in summer. A life-threatening exacerbation of LP in this patient was reported previously.<sup>7</sup> Several small haemorrhagic crusts, measuring 3–5 mm in diameter, had been observed at almost every visit.

On examination, small clear vesicles were observed on normal skin. There were also quite large eroded lesions (Fig. 1a). Sheets of necrotic epidermis had slipped off these lesions, leaving red oozing erosions (Fig. 1b). During follow-

up, vesicles ruptured rapidly, erosions formed and they continued to spread. However, most of the lesions did not show blisters and had a steadier pattern of shedding. The erosions had a tendency to develop excessive crusting. Thick haemorrhagic crusts developed as the lesions evolved, and they healed leaving depressed scars (Fig. 1c). Healing took place over 20 or more days. The lesions favoured the proximal upper extremities, upper trunk and face.

A biopsy was obtained from the lesion shown in Fig. 1(a). The epidermis was atrophic, and haematoxylin and eosin staining showed an expanded papillary dermis with homogeneous pink material. The amorphous protein was deposited around blood vessels and as thick bundles perpendicular to the skin surface. The tips of the dermal papillae were extremely narrowed and often eroded, with the base consisting of amorphous material (Fig. 1d). Parakeratosis and intracorneal polymorphonuclear leucocytes and extravasated erythrocytes were also seen. The papillary dermis and thickened blood vessels stained positive with periodic acid-Schiff (PAS). Amyloid stain was negative.

Treatment was given with oral prednisolone 15 mg daily ( $1 \text{ mg kg}^{-1}$ ) and a combination of topical 0.1% diflucortolone-2-valerate + 1% chlorquinaldol cream twice daily. After



**Figure 1.** (a) Clear vesicles and erosions on the left arm. (b) Sheets of necrotic epidermis slipped off, leaving red oozing erosions. (c) Ulcers with thick haemorrhagic crusts leaving depressed scars. (d) The tips of the dermal papillae were extremely narrowed and often eroded, with the base consisting of amorphous material (haematoxylin and eosin; original magnification  $\times 100$ ).

10 days, new lesion development ceased and the oral prednisolone was tapered and stopped. When the erosions evolved into haemorrhagic crusted ulcers we replaced the topical corticosteroid treatment with 1% silver sulphadiazine cream twice daily until complete healing was achieved. The patient is still in our follow-up, and for new individual lesions she is applying 0.1% diflucortolone-2-valerate + 1% chlorquinaldol cream twice daily for 5 days, followed by 1% silver sulphadiazine cream twice daily until the lesions are completely healed. Her parents stated that this treatment accelerated healing and that the scars of the lesions were cosmetically more acceptable.

We observed the evolution of the first stage lesions of LP in our patient. Small vesicles arose spontaneously on normal skin and were clear and noninflamed. Large sheets of skin were shed, just as from a burn, leaving red oozing erosions; however, flaccid bullae were not a prominent feature. The vesicles ruptured rapidly and erosions formed, but most of the lesions did not show blisters and had a steadier pattern of shedding. The erosions had a tendency to develop excessive crusting. Ulcers with thick haemorrhagic crusts appeared as the lesions evolved, and they healed leaving depressed scars.

The precise pathogenesis of LP is not understood. Specific overproduction of basement membrane type IV collagen by epithelial or endothelial cells and increased synthesis of noncollagenous glycoproteins by fibroblasts appear to be important in the pathogenesis.<sup>8,9</sup> Histologically, lesions of LP are characterized by depositions of extracellular and perivascular PAS-positive and diastase-resistant amorphous material. Haematoxylin and eosin staining of the lesions reveals pale pink, hyaline-like depositions especially in the papillary dermis and around dermal capillaries. The early inflammatory stage has not been well characterized histologically. In the second stage, deposits increase in the dermis and the skin becomes thickened and waxy.<sup>3,5</sup> In our case, the epidermis was atrophic and the papillary dermis was expanded with homogeneous pink material. The amorphous material was deposited around blood vessels and as thick bundles perpendicular to the skin surface. The tips of the dermal papillae were extremely narrowed and often eroded, with the base consisting of amorphous material. We suggest that a possible abrupt increase in the amorphous mass might be the cause of epidermal atrophy; erosions and ulcerations might be due to the blockage of the capillary circulation in the papillary dermis as a result of perivascular depositions. Furthermore, the rapid invasion of the papillary dermis and basal membranes with amorphous material might result in mechanical damage to the tissues.

The treatment of LP remains frustrating. The case for early systemic corticosteroid therapy in the first stage is still unproven.<sup>10</sup> Although development of new lesions ceased after the introduction of systemic corticosteroid treatment in our patient, we do not know whether this improvement was due to our treatment, as the disease shows a fluctuating course. However, individual lesions appeared to be improved with potent topical corticosteroid treatment.

We highlight the clinicopathological features of the early erosive vesicular stage of LP. These findings may help in understanding the disease process and pathogenesis of LP. According to our findings, systemic and topical corticosteroid treatment is worth trying in early lesions of LP.

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## Book reviews

**Color Textbook of Pediatric Dermatology, 3rd edn.** (2002). W.WESTON, A.LANE and J.MORELLI. St Louis: Mosby Inc. ISBN 0323018211, 369 pp. Price 70.00

This third edition of the *Color Textbook of Pediatric Dermatology* is a highly readable book with excellent clinical photographs. Each chapter tackles the standard dermatological problems and is subdivided further into individual conditions which are discussed under the headings of clinical features, differential diagnosis, pathogenesis, treatment, patient education and suggested follow up. The style, with green headings, boxed information, and tabulated lists, allows easy reading. It is compact but comprehensive. The photographs are of notable clarity and the references at the end of each chapter are impressively up to date.

All relevant topics are covered in practical detail in the 22 chapters. The chapter on Dermatopharmacology and Topical Formulary is informative although American trade names are used, this section obviously being aimed at the US reader. The Appendix contains patient instructions, which the reader is invited to photocopy for use in clinical practice. The advice is standard in most examples although there are differences between North American and UK practice. These are perhaps highlighted in the treatment for molluscum with imiquimod, and wet-wrap dressings for atopic eczema comprising of 1 wet pair of pyjamas with a dry pair on top. This tip could certainly reduce the NHS wet-wrap bandage bill!

A problem-orientated differential diagnosis index inside the front and back covers, listed in order from the commonest to the rarest, is a further useful guide. The standard index appears comprehensive.

The book has been written for clinicians responsible for the primary care of children. It should certainly be most helpful to the UK dermatology SpR in training and to any dermatologist interested in paediatric dermatology. This is a readable, informative and well-illustrated resource, which at 70 is a bargain.

AILEEN TAYLOR

**PDQ Oral Disease. Diagnosis and Management** (2002). J.J.SCIUBBA, J.A.REGELZ, R.S.ROGERS III. Hamilton, Ontario: BC Decker. ISBN 1550092189, 384 pp. Price 59.99; 39.99.

This is one of several books in the PDQ series, which stands for 'pretty darned quick', an instant giveaway that the origins are in North America. Its primary aim is to help clinicians reach a quick diagnosis when faced with a patient who has a disease of the oral cavity and jaws. It is written by a dermatologist, an ENT surgeon and an oral pathologist.

It is a well-illustrated text with clinical pictures of all the diseases discussed. In general, these are of good quality with some impressive intra-oral close-ups. The hairy tongue on page 15 is particularly spectacular! Unfortunately, there are no figure legends, which would have been useful, particularly for those figures where the area of interest is not clear.

The layout is ideal for a quick reference text, with subheadings and division of the text into bite-sized chunks using bullet-points. The book is further divided into sections according to the clinical presentation, such as ulcerative conditions and pigmentary disorders, which is logical for a book in which the first goal is to make the diagnosis and on the whole, this approach works well. However, it's not always obvious where to start. For example, there are separate vesicobullous disease and ulcerative conditions sections, and if faced with a patient who has a swollen lip, angioedema and cheilitis granulomatosa are in the inflammatory diseases section while Melkersson-Rosenthal syndrome is with the connective tissue lesions. In addition, there is no alphabetical index to guide the reader when starting from the diagnosis rather than the clinical presentation.

The information provided on each topic is brief, practical and summarises each topic in a nutshell, entirely appropriate for a quick reference text. The reader would have to look elsewhere for more in-depth information and with this in mind, the authors provide an additional reading section where up-to-date references are listed. There is also a separate therapeutics section with more detailed information than that provided in the main body of the book.

As a dermatologist, some sections of the book are unlikely to be useful, such as the odontogenic tumours. However, many of the diagnoses discussed are likely to be encountered occasionally and a text covering oral medicine, such as this, would be a useful addition to the dermatologist's library. Being pocket-sized, it would not take up much space on the bookshelf and each volume comes with a copy on CD-ROM. Whether there are better rival books on the market, I cannot comment and 60 seems overpriced for a pocket-sized paperback. Therefore, it might be better investment to put the money towards a major textbook of oral medicine. Nevertheless, I could imagine dermatologists and trainees dipping into this quick reference text according to the patients they've seen and finding it a helpful first port of call.

KAREN HARMAN

## News and Notices

**43rd Congress of the German Dermatological Society (Deutsche Dermatologische Gesellschaft DDG) in Berlin, Germany, 6–11 May 2003.**

For further information contact: Beiersdorf AG, Research and Development cosmed, Dept. 4210, Unnastrasse 48, D-20245 Hamburg, Germany.

**First Joint Meeting of the 14th International Congress for Bioengineering and the Skin and the 8th Congress of the International Society for Skin Imaging 21–24 May 2003**

Current information and registration can be obtained from: <http://www.AKM.ch/ISBS/ISS12003>, or from the chairman of the organizing committee: Dr K-P.Wilhelm, Conference Secretariat, AKM Congress Service GmbH, HauptstraBe 18, 79576 Weil am Rhein, Germany.

**Third World Congress of the International Academy of Cosmetic Dermatology 14–17 May 2003, Beijing, China**

The conference will take place under the auspices of the International Academy of Cosmetic Dermatology, organized by Chinese Medical Meetings International and the Chinese Society of Medical Esthetics & Cosmetology. This event will gather specialists to discuss all aspects of cosmetic dermatology. Topics include: basic science of cosmetic dermatology, photodermatoses and sun screen, skin care, cosmetic dermatosurgery, laser therapy, skin resurfacing, acne, pigmented disorders, and hair and nail disorders.

For further information please contact: IACD2003 Secretariat, Chinese Medical Meetings Internations, 42 Dongsi Xidajie, Beijing 100710, China. Tel.: + 86 6512 2268, ext. 1604/1606/1608; fax: + 86 6524 4086; e-mail: [iacd2003@chinamed.com.cn](mailto:iacd2003@chinamed.com.cn). The website is at: <http://www.chinamed.com.cn/iacd>