British Journal of Dermatology 2001; **144:** 1086–1099.

Correspondence

Acrogeric phenotype in Ehlers–Danlos syndrome type IV attributed to a missense mutation in the COL3A1 gene

SIR, The Ehlers–Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility, and tissue fragility. Type IV (EDSIV), the ecchymotic or vascular type, is a rare EDS subtype which is characterized by spontaneous vascular rupture and bowel perforation. The disease is generally inherited in an autosomal dominant fashion, but frequently there may be single affected individuals in families; it has been proposed that autosomal recessive forms also exist.[1] The gene for EDSIV has been identified as the COL3A1 gene, located at 2q31–q32, encoding the chains of type III procollagen.[2]

A 31-year-old white female was referred to our department with suspected EDSIV. She was the second child of unrelated parents. After a normal pregnancy, she was born prematurely at 24 weeks' gestation weighing 1750 g. She failed to thrive and remained in an incubator for 2 months. At the time of delivery, her father was aged 40 years and her mother 39 years. No other members of the family were reported to be affected by skin problems. The patient's skin changes and articular hypermobility were noted immediately after birth. A tendency toward easy bruising and bleeding was noted when she was 6 years old. At the age of 14 years, marked shortening of the right achilles tendon causing talipes equinovarus was noted. In addition, she had a history of recurrent bilateral pneumothoraces treated by pleural stripping when she was 19 years old. At the age of 29 years there was a subarachnoidal haemorrhage due to rupture of an intracranial aneurysm.

On physical examination, she had a thin, pinched, curved nose, thin lips, tight skin, hollow cheeks, and large prominent eyes. Tight, firm, lobeless ears were also present. There was prominent capillary telangiectasia and prominent venules over her upper anterior chest (Fig. 1). The skin on the dorsum of her hands was thin and had a prematurely aged appearance. Acrocyanosis of both hands was also noted. Mild hyperextensibility of the digits, hands, and elbows was present. Cardiological examination revealed low-grade pulmonary valve stenosis and mitral valve prolapse with thickening and prolapse of the anterior mitral valve leaflet. A skin biopsy from the left hand showed both collagen depletion and relative elastic fibre accumulation with shortening and fragmentation.

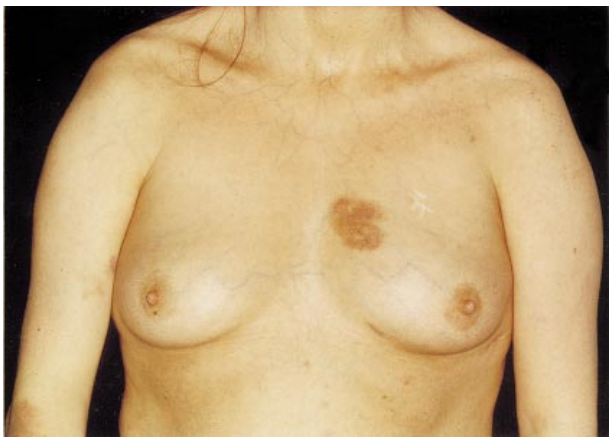

Figure 1. The anterior aspect of the chest showing transparent skin with an obvious venous pattern. Ecchymosis from minimal trauma is also seen.

Biochemical analysis by sodium dodecyl sulphatase–polyacrylamide gel electrophoresis showed decreased secretion of collagen type III by skin fibroblasts from the patient (Fig. 2). Separation of the collagen molecules retained in the cell layer showed an accumulation of collagen type III chains that migrated with a slight smear, which could indicate the presence of slower migrating, mutant collagen type III molecules. In addition to these findings there was an additional band right above the band representing the α2(V) collagen chains. *In situ* cyanogen bromide digestion and electrophoresis in the second dimension confirmed that

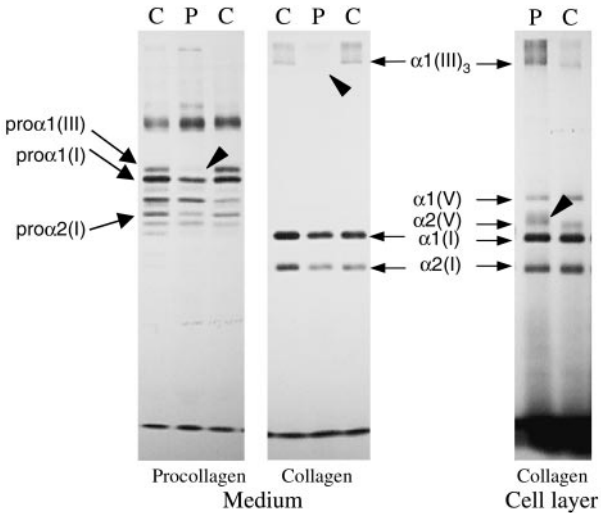

Figure 2. Biochemical analysis (P, patient; C, control). Sodium dodecyl sulphate–polyacrylamide gel electrophoresis analysis of (pro-) collagen produced by skin fibroblasts from the patient with EDSIV showing procollagen secreted in the medium (left panel), pepsin-derived procollagen secreted in the medium (middle panel), and collagen retained in the cell layer (right panel). Left panel: there is a diminished secretion of proα1(III) cells in the medium. Middle panel: as the α1(III) chain contains a cysteine residue, trimers are seen high above in the gel. In the middle lane, diminished collagen type III is seen. Right panel: in the left lane, there is a marked accumulation of collagen type III molecules which are retained in the cell layer. Above the α2(V) band, an additional band is visible.

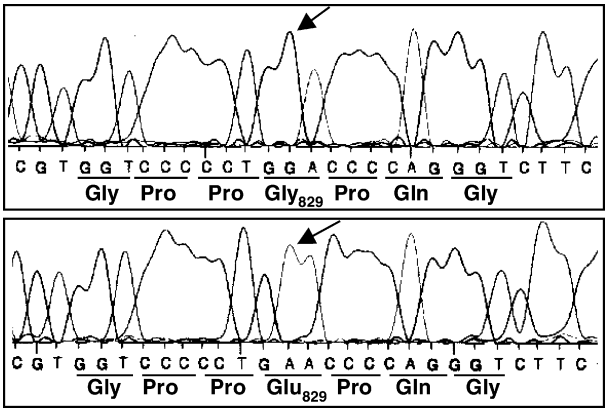

Figure 3. Sequencing data of the normal (upper panel) and the mutant (lower panel) COL3A1 allele from the patient with EDSIV. In the middle, a G–>A transversion is seen in the mutant sequence. The base change is present in half of the sequenced clones. As a consequence, a glutamate residue is incorporated instead of a glycine residue at this particular site.

this extra band was composed of mutant α1(III) monomers (data not shown).

Molecular studies by heteroduplex analysis of the COL3A1 cDNA revealed an abnormal fragment covering the region from exon 41–46 (Fig. 3). Cloning and sequencing of this fragment revealed a heterozygous G to A transition in exon 42 resulting in the substitution of a glycine (GGA) in position 829 of the proα1(III) chain for a glutamate (GAA). This mutation created an additional restriction site for the enzyme *Ava*II. Restriction digestion of the cDNA confirmed the heterozygous state of the mutation.

EDSIV is caused by an abnormality of collagen type III as a result of mutations in the COL3A1 gene. A collagen type III abnormality is also seen in patients with Ehlers–Danlos syndrome without the classical severe EDSIV phenotype.[3] There is no correlation between the nature of the COL3A1 mutation and the severity of the clinical phenotype.

A variety of mutations have been identified within the triple-helical coding region of the COL3A1 gene, which encodes the α1 chain of collagen type III.[2,4] Glycine substitutions and exon skips are the commonest mutations although variable deletions have also been described. The acrogeric phenotype is usually seen with 3′ mutations whereas the phenotypes of 5′ or middle helical exon skips are more difficult to recognize. The causal mutation in our patient was a missense mutation resulting in the substitution of a glycine residue in position 829 of the α1(III) collagen chain by glutamic acid (G829E). As a consequence, collagen type III trimers accumulated in the cell layer where a proportion of mutant collagen type III molecules ran as overhydroxylated monomers. Most probably, the glycine substitution prevents the formation of this SS-bridge at position 1012 in the extreme C-terminal end of the α1(III) helix.[5] Formation of this SS-bridge is important for nucleation and trimerization of the proα1(III) collagen chains. The same unusual collagen pattern has been observed in association with a G1009V[6] and a G1006R (personal communication) substitution, respectively. While for those mutations this can easily be explained by the proximity of the mutation to the cysteine residue in position 1012 involved in the SS-bridge, this relationship is less clear for the G829E substitution. Possibly, the presence of this mutation changes the secondary structure of the collagen chains in a way that the formation of the SS-bridge is prevented.

Department of Dermatology and Allergology, Ruhr-University Bochum, Gudrunstrasse 56, D-44791 Bochum, Germany, T. JANSEN
**Center of Medical Genetics, Ghent, Belgium* A. DE.PAEPE*, L. NUYTINCK*, P. ALTMEYER
Correspondence: Thomas Jansen, M.D.
E-mail: Bochum@derma.de

References

1 Pope FM, Martin GR, McKusick VA. Inheritance of Ehlers–Danlos type IV syndrome. *J Med Genet* 1977; **14**: 200–4.
2 Byers PH. Ehlers–Danlos syndrome: recent advances and current understanding of the clinical and genetic heterogeneity. *J Invest Dermatol* 1994; **103** (Suppl.): 47S–52S.
3 Hamel BC, Pals G, Engels CH *et al.* Ehlers–Danlos syndrome and type III collagen abnormalities: a variable clinical spectrum. *Clin Genet* 1998; **53**: 440–6.
4 Johnson PH, Richards AJ, Lloyd JC *et al.* Efficient strategy for the detection of mutations in acrogeric Ehlers–Danlos syndrome type IV. *Hum Mutat* 1995; **6**: 336–42.
5 Steinmann B, Superti-Furga A, Joller-Jemelka HI *et al.* Ehlers–Danlos syndrome type IV. a subset of patients distinguished by low serum levels of the amino-terminal propeptide of type III procollagen. *Am J Med Genet* 1989; **34**: 68–71.
6 Nuytinck L, De Paepe A, Renard JP *et al.* Single-strand conformation polymorphism (SSCP) analysis of the COL3A1 gene detects a mutation that results in the substitution of glycine 1009 to valine and causes severe Ehlers–Danlos syndrome type IV. *Hum Mutat* 1994; **3**: 268–74.

Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis

SIR, We read with interest the report of two cases with hypereosinophilic syndrome (HES), digital gangrene, and skin lesions referred to as eosinophilic cutaneous vasculitis by Jang *et al.*[1] We observed a similar case who presented with angiographically documented occlusion of medium-sized arteries.

A 48-year-old, nonsmoking male was diagnosed with cholinergic urticaria 30 years ago and Widal's syndrome (nasal polyps, asthma, intolerance of non-steroidal anti-inflammatory drugs) 6 years ago. Since then he has continuously received inhaled β2 stimulants and nasal corticosteroids (fluticasone > 500 μg daily) as well as anti-H1- and

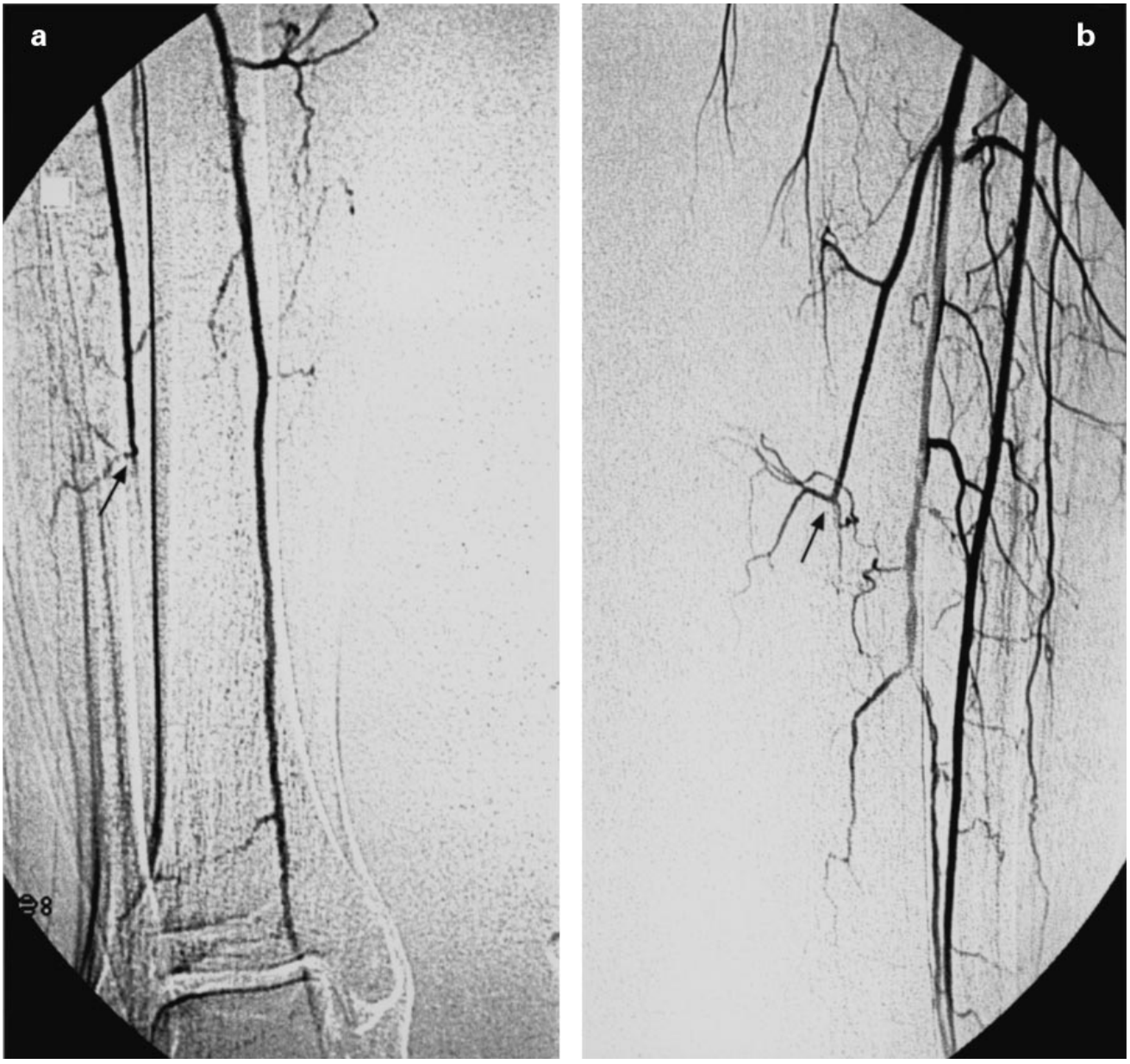

Figure 1. Arrows point to the occlusions in the right peroneal artery (a) and the left posterior tibial artery (b), respectively.

H2-blocking drugs intermittently. Four years ago, he had epigastric pain diagnosed on biopsy as eosinophilic gastritis. Since then he has received oral prednisone (12·5–30 mg daily). A nodule of 2 × 2 cm in the right masseter area was identified in the same year. A fine needle aspiration of the lesion yielded 15 mL blood.

Three years ago, he presented with purpuric urticarial plaques. A biopsy revealed leukocytoclastic vasculitis of the superficial dermis with a few eosinophils in the perivascular mixed neutrophilic–mononuclear cell infiltrate; there were no extravascular granulomas or giant cells. Urticarial vasculitis was diagnosed. The skin lesions disappeared with thalidomide (200 mg daily) and did not recur after cessation of this drug. In the same year the patient had colonic surgery for diverticulosis previously diagnosed by coloscopy. The histological diagnosis was 'eosinophilic diverticulitis'. Twenty-seven months ago, he began to suffer from Raynaud's phenomenon of both hands and subsequently developed multiple splinter haemorrhages and bland purpuric macules of the fingertips which developed into necrotic ulcers up to 1 cm in diameter. No clinical sign of cutaneous vasculitis was identified. Allen's test was bilaterally pathological. Occlusion of several digital arteries (left: digits II, III; right: digits III, IV, V) as well as the cubital arteries was suspected as a result of arterial pressure measurements taken at various levels followed by laser Doppler and photoplethysmographic examination. Administration of

iloprost infusions and ticlopidine (250 mg twice daily) was followed by subjective improvement. The skin lesions healed with scarring. Three months later, he developed claudication of both lower extremities. The lower extremities were cold but without necrosis. Stage IIa arterial insufficiency was diagnosed and arterial occlusion confirmed by laser Doppler examination. Angiography of the lower extremities showed occlusion of the right peroneal artery and the left posterior tibial artery (Fig. 1). The remainder of the clinical examination was normal, including neurological and ophthalmological evaluation. The patient was given iloprost intravenously with relief of symptoms. Prednisone (12·5 mg daily) and topical corticosteroids were continued. Since then he has had no relapse of the vascular symptoms.

Laboratory investigations revealed blood eosinophilia that varied between 1972 and 10 164 GL^{-1} in the last 3 years, with the red blood cell count and the remainder of the white cell count always normal. IgE was 62–269 kU L^{-1}, ECP 62–> 200 μg mL^{-1} (normal 2·3–16 μg mL^{-1}). Other blood chemistry tests including electrolytes, urinalysis and renal clearance, were normal. Numerous investigations for eosinophilia, including repeated searches for parasites in the stool and parasite serology, were negative. Serology for parvovirus B19 was IgM negative and IgG weakly positive. A VDRL test was negative. Immunological screening tests including antinuclear, anticentromere, anti-dsDNA, anticardiolipin, and anti-Jo1 antibodies, ANCA, complement (C3, C4, CH50, C3d), serum protein electrophoresis, immunoelectrophoresis, immunofixation and cryoglobulins were negative. Skin prick tests to numerous food and aeroallergens were negative. Coagulation parameters including proteins C and S were normal. Several bone marrow smears and biopsies showed up to 31% eosinophils but no other abnormality. No signs of a clonal T cell population or any surface marker abnormality in blood T cells was identified (tests performed by Dr H-U.Simon, Schweizerisches Institut für Allergie-und Asthmaforschung, Davos, Switzerland[2]). Repeated echocardiographic examinations, chest X-rays and thoracoabdominal CT scans were normal. NMR examination of the masseterian mass revealed a vascular intraparotid tumour. Biopsy of this lesion was refused by ENT staff because of its proximity to the facial nerve. Angiography of the coeliac axis and the superior mesenteric artery as well as repeated electromyographic examinations were normal.

Our patient's condition is compatible with HES,[3] although we were unable to identify any of the reported T-cell abnormalities.[2,4] It also fulfils the American College of Rheumatology criteria of Churg–Strauss syndrome.[5] In this case, he would present an atypical form due to the absence of pulmonary infiltrates, polyneuropathy, arthritis, fever, myalgia and pANCA, all of which are typical features of this condition. Cutaneous infarction and digital necrosis have been reported in Churg–Strauss syndrome.[6–9] In turn, asthma is not common in HES.[3] Kimura's disease cannot be fully excluded in the absence of a biopsy of the intraparotid vascular lesion but is unlikely as the most frequent systemic involvement in this disorder, aside from blood eosinophilia, is renal.

It is not clear whether the first case reported by Jang *et al.*[1] had venous or arterial thrombi, or both. Venous thrombosis has been reported in HES.[3] Arterial thrombi may explain digital gangrene better than cutaneous vasculitic lesions alone. As mentioned by Jang *et al*. digital gangrene has only rarely been reported in HES.[1] In our case, we demonstrated arterial occlusions in both the upper and lower extremities by angiography. We could not identify the precise nature of the arterial lesion in our patient because a biopsy of the arteries was refused. Such arterial lesions have previously been described as corresponding to arteritis containing eosinophils in the inflammatory infiltrate of the vessel wall with secondary thrombosis[10] or to thrombi without underlying vasculitis.[11] Our case did not have any other skin lesions concomitant with the digital necrosis, demonstrating that digital necrosis in HES can occur independent of cutaneous (eosinophilic) vasculitis. The episode of urticarial vasculitis 2 years prior to digital necrosis was not associated with a predominance of eosinophils in the perivascular infiltrate.

In conclusion, our case demonstrates that digital necrosis in HES can be associated with occlusion of medium-sized arteries but without cutaneous (eosinophilic) vasculitis. Thus, occlusion of medium-sized arteries should be sought in patients with HES and digital necrosis.

*Division of Allergy and Immunology and
†Department of Dermatology,
Hôpital Cantonal Universitaire
1211 Geneva 14, Switzerland
‡Institut Central des Hôpitaux Valaisans,
1950 Sion, Switzerland

R. Oppliger*
F. Gay-Crosier*
E. Dayer‡
C. Hauser*‡

References

1 Jang KA, Lim YS, Choi JH *et al.* Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. *Br J Dermatol* 2000; **143**: 641–4.
2 Simon HU, Plotz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med* 1999; **341**: 1112–20.
3 Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood* 1994; **83**: 2759–79.
4 Cogan E, Schandene L, Crusiaux A *et al.* Clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. *N Engl J Med* 1994; **330**: 535–8.
5 Cottin V, Cordier JF. Churg–Struass syndrome. *Allergy* 1999; **54**: 535–51.
6 Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg–Strauss syndrome: a clinicopathologic correlation. *J Am Acad Dermatol* 1997; **37**: 199–203.
7 Gibson LE. Granulomatous vasculitides and the skin. *Dermatol Clin* 1990; **8**: 335–45.
8 Crotty CP, DeRemee RA, Winkelmann RK. Cutaneous clinicopathologic correlation of allergic granulomatosis. *J Am Acad Dermatol* 1981; **5**: 571–81.
9 Lhote F, Cohen P, Guillevin L. Syndrome de Churg et Strauss. In: *Maladies et Syndromes Systémiques* (Kahn MF, Peltier AP, Meyer O, Piette JC, eds). 4th edn. Paris: Flammarion. 2000: 725–40.

10 Hachulla E, Hatron PY, Janin A *et al.* Arterite digital, thrombose et syndrome hypereosinophilique: une complication exceptionnelle. *Rev Med Interne* 1995; **16**: 434–6.
11 Liozon E, Delaire L, Lacroix P *et al.* Syndrome de Raynaud compliqué de gangrene digitale au cours d'un traitement par l'interféron alpha. *Rev Med Interne* 1997; **18**: 316–19.

Pityriasis rosea: one virus, two viruses, more viruses?

SIR, We read with interest the recent report by Kosuge *et al*. on the prevalence of human herpesvirus (HHV)-6 and HHV-7 in pityriasis rosea (PR)[1] and we fully agree with them that differences in the time of collection of tissue samples may often explain the different results reported, and that many causative agents may cause the same exanthem. Moreover, having originated the controversy on the HHV aetiology of PR,[2] we would like to comment on the attempt to attribute an aetiological role to HHVs in a particular disease.

HHVs share the unique property of establishing a state of latent infection, and peripheral blood mononuclear cells (PBMCs) may be one of the sites of such latency. As a consequence, detecting HHV DNA in PBMCs is of limited diagnostic utility. It may indicate the presence, but not necessarily the activity, of the virus. In addition, the wide range of polymerase chain reaction (PCR) positivity on PBMCs reported by several studies may depend on the different sensitivities of PCR and/or on the different geographical prevalence.

Kosuge *et al*. detected HHV-7 DNA by PCR in the PBMCs in 43% of PR patients and in 56% of the controls, and HHV-6 DNA in 21% of the patients and 39% of the controls.[1] Although their controls were patients with skin diseases other than PR and not healthy people, their detection rate is comparable with ours. PBMCs of patients with PR have previously been documented to harbour HHV DNA. Yasukawa *et al.*,[3] for example, detected HHV-6 in 43% of 14 PR patients and HHV-7 in 7%, but surprisingly failed to detect HHV DNA in PBMCs of control individuals, a fact that is in conflict with the widespread detection of HHVs in the general population. In fact, HHV-6 has been recovered from PBMCs in 17–90% of healthy subjects, and HHV-7 in over 80%. What matters, therefore, is finding markers of viral replication such as detecting in PBMCs those antigens which are expressed during a lytic infection, or detecting HHV DNA in plasma, as we did in 100%[2] and Watanabe *et al.*[4] in almost 50% of PR cases.

Care should be taken in interpretation of serological studies that attribute a causal role to a virus, especially when its seroprevalence in the general population is high. There are many reasons to be cautious in this regard. A positive result of specific serology indicates that contact with the virus has occurred, but by no means indicates its state of activity. HHVs are antigenically related and cross-reactive antibodies can be boosted. For example, simultaneous increases in seroreactivity for both HHV-6 and cytomegalovirus have been observed[5] and, for HHV-6 and HHV-7, the titre of antibodies to one virus may rise during the seroconversion to the other. Traditionally, relating an acute illness to HHV infection requires the occurrence of specific IgM antibodies or a fourfold or greater variation of the IgG antibody titre in the time-separated paired specimens. The presence of IgM antibody alone cannot be considered a reliable marker for HHV-6 infection because most cases, confirmed by culture or by IgG seroconversion at high titre, had no detectable IgM response and approximately 5% of adults are IgM positive at any time.

Finally, all studies suggesting a pathogenetic role of HHV-6 and HHV-7 should take into account the possibility that HHV-6 can be reactivated by a HHV-7 infection or reactivation.[6] Some HHV-7 genes may transactivate those of HHV-6 and may stimulate HHV-6 replication and reactivation. Furthermore, once reactivated, latent HHV-6 genomes may become prominent, leading to the disappearance of those of HHV-7 or impairing their detection by PCR and serology. This may explain why HHV-6 may be easily isolated from PBMCs after HHV-7 reactivation and also why other HHV-6 antigens can be boosted by HHV-7 infection and may be detected in skin and PBMCs.

In conclusion, we suggest extreme caution in attributing PR or other skin conditions exclusively to HHV-6 because it is fully possible that HHV-7 infection can be hidden from both PCR and serology.

Department of Endochronologic and Metabolic Diseases, Clinica Dermatologica, University of Genoa, Viale Benedetto XV, 7, 16132 Genova, Italy

F. DRAGO
A. REBORA

References

1 Kosuge H, Tanaka-Taya K, Miyoshi H *et al.* Epidemiological study of human herpesvirus-6 and human herpesvirus-7 in pityriasis rosea. *Br J Dermatol* 2000; **143**: 795–8.
2 Drago F, Ranieri E, Malaguti F. Human herpesvirus in pityriasis rosea. *Lancet* 1997; **349**: 1367–8.
3 Yasukawa M, Sada E, MacHino H, Fujita S. Reactivation of human herpesvirus 6 in pityriasis rosea. *Br J Dermatol* 1999; **140**: 169–70.
4 Watanabe T, Sugaya M, Nakamura K, Tamaki K. Human herpesvirus 7 and pityriasis rosea. *J Invest Dermatol* 1999; **113**: 288–9.
5 Efstathiou S, Gompels UA, Craxton MA *et al.* DNA homology between a novel human herpesvirus (HHV-6) and human cytomegalovirus. *Lancet* 1988; **1**: 63–4.
6 Tanaka-Taya K, Kondo T, Nakagawa N *et al.* Reactivation of human herpesvirus 6 by infection of human herpesvirus 7. *J Med Virol* 2000; **60**: 284–9.

Trichoblastoma with sebaceous and sweat gland differentiation

SIR, Trichoblastoma is a rare, benign tumour of hair germ that has variable histological findings. Although several cases of trichoblastoma have been described, trichoblastoma showing multiple differentiation towards more than one type

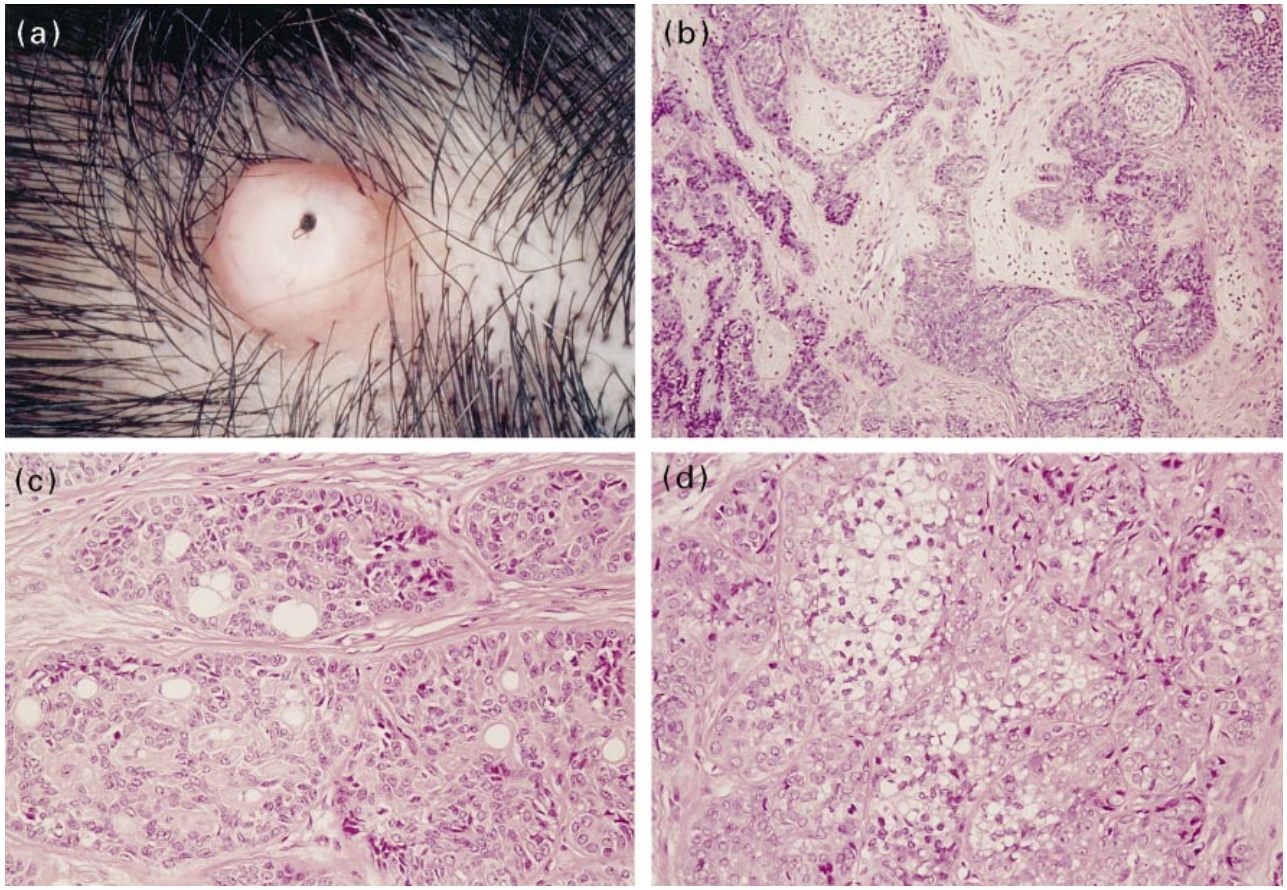

Figure 1. (a) A single, well-defined, 1·5-cm firm pedunculated nodule with central follicular plugging is evident on the vertex of the scalp. (b) Reticulation patterns of narrow branching cords and many cell balls in which basaloid cells form densely packed, rounded nests. (c) Many sebocytes with compact nuclei and abundant multivacuolated lucent cytoplasm. (d) Multiple lobules of uniform polygonal cells containing multiple eosinophilic hyaline material (haematoxylin and eosin; original magnifications: b, × 100; c, × 400; d, × 400).

of adnexal structure is rare, with very few well-documented cases reported in the literature.

A 50-year-old woman, otherwise well, presented with a 4-year history of a slowly enlarging nodule on the vertex of the scalp. Examination revealed a 1·5-cm pedunculated nodule that had a firm consistency, spherical morphology and a well-marginated, smooth surface without ulceration (Fig. 1a). There was no tenderness and no lymphadenopathy. Histology of the excised lesion revealed a single well-demarcated tumour mass in the dermis and subcutaneous tissue. This contained multiple lobules which were composed of basaloid cells displaying various patterns of large nodules, small nodules and reticulation (or narrow branching cords). Retraction spaces between the basaloid cells and stroma were not observed. Within the lobules, the basaloid cells formed numerous densely packed, rounded nests, so-called 'cell balls' (Fig. 1b). The neoplastic cells showed no evidence of atypia, and mitoses and apoptotic cells were not found. In some areas, sebocytes with compact nuclei and abundant multivacuolated lucent cytoplasm were found (Fig. 1c). These cells formed either small aggregates or single units within the tumour lobules, and they were interpreted as an expression of sebaceous differentiation. Other areas were composed of lobules of uniform polygonal cells which were smaller than keratinocytes, and contained multiple areas of eosinophilic hyaline material (Fig. 1d). This material was accentuated by periodic acid–Schiff staining, and these areas were interpreted as an expression of cutaneous glandular (eccrine or apocrine) differentiation even though immunohistochemical stains for carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) were negative, and definite tubular structures were not seen. Cytokeratin was expressed in all tumour cells, whereas stains for S-100, CEA, EMA and CD34 were negative. Some neoplastic cells showed positivity for vimentin.

Trichogenic tumours are uncommon benign neoplasms derived from hair germ cells which develop into hair follicles.[1–3] The histogenesis of trichogenic tumours is complex; a firm classification of these tumours remains to be established and several diagnostic terms have been proposed.[4–7] Ackerman *et al.*[3] suggested that 'trichoblastoma' should be used as an inclusive term for all benign cutaneous tumours that are composed mostly of follicular germinative cells.

In our case, the tumour mass consisted of several histological patterns, such as large nodules, small nodules and reticulation. Many 'cell balls' (masses of basaloid cells forming numerous densely packed, rounded nests) were observed, and an exceptional finding was the presence of areas showing sebaceous and sweat gland differentiation within the tumour. In areas of sebaceous differentiation, the sebocytes had a characteristic morphology with compact nuclei and abundant multivacuolated lucent cytoplasm; these cells were found either as small aggregates or as single units within the tumour lobules. In the sweat gland areas we think that the apocrine line of differentiation is more reasonable than the eccrine, because its association with sebaceous cells recapitulates the normal development of the apocrine-pilosebaceous apparatus.[8] Embryologically, apocrine glands develop from the upper bulge of the hair follicle, in contrast to eccrine glands which develop from the basal layer of the epidermis. However, the immunohistochemistry performed could not distinguish between apocrine and eccrine differentiation.

Department of Dermatology and Pathology, S.N.CHANG
Inje University Ilsan Paik Hospital, Y.L.CHUNG*
Seoul, Korea S-C.KIM*
**Department of Dermatology,* J.Y.SIM†
Yonsei University College of Medicine, W.H.PARK†
Yongdong Severance Hospital,
146–92 Dogok-dong,
Kangnam-gu,
Seoul 135–720, Korea
†*Pochon CHA University Pundang CHA Hospital, Seoul, Korea*
Correspondence: Yae Lee Chung.
E-mail: ylchung@hanmail.net

References

1 Headington JT. Differentiating neoplasm of hair germ. *J Clin Pathol* 1970; **23**: 464–71.
2 Headington JT. Tumors of hair follicle: a review. *Am J Pathol* 1976; **85**: 480–505.
3 Ackerman AB, de Viragh PA, Chongchitnant N. Trichoblastoma. In: *Neoplasms with Follicular Differentiation* (Ackerman AB, de Viragh PA, Chongchitnant N, eds). Philadelphia: Lea & Febiger. 1993: 357–472.
4 Rosen LB. A review and proposed new classification of benign acquired neoplasm with hair follicle differentiation. *Am J Dermatopathol* 1990; **12**: 496–516.
5 Wick MR, Swanson PE, Barnhill RL. Sebaceous and pilar tumors. In: *Textbook of Dermatopathology* (Barnhill RL, Busam KJ, Crowson AN *et al.*, eds), 1st edn. New York: McGraw-Hill. 1998: 593–621.
6 Headington JT. Tumors of hair follicle differentiation. In: *Pathology of the Skin* (Farmer ER, Hood AF, eds), 2nd edn. New York: McGraw-Hill. 2000: 1008–18.
7 Elder D, Elenitsas R, Ragsdale BD. Tumors of the epidermal appendage. In: *Lever's Histopathology of the Skin* (Elder D, Elenitsas R, Jaworsky C, Johnson B Jr, eds), 8th edn. Philadelphia: Lippincott-Raven. 1997: 596–604.
8 Zaim MF. Sebocrine adenoma: an adnexal adenoma with sebaceous and apocrine poroma-like differentiation. *Am J Dermatopathol* 1988; **10**: 311–8.

Cutaneous presentation of chronic lymphatic leukaemia and response to ultraviolet B phototherapy

SIR, A 59-year-old man presented in 1988 following a holiday in India where he had rapidly developed painful nodules on his ears and nose. He had no past medical history of note, no systemic symptoms, nor was he taking any oral medications. He had a family history of chronic lymphatic leukaemia (CLL; sister and first cousin). Examination revealed tender, infiltrated, red-brown nodules and plaques crowded around the helix of both pinnae and his nose. There was no visceral organomegaly nor any palpable lymphadenopathy.

He had a haemoglobin of 14 g dL^{-1}, white cell count $13{\cdot}2 \times 10^9$ L^{-1} (lymphocytes $9{\cdot}7 \times 10$ L^{-1}) and platelet count 190×10^9 L^{-1}. A skin biopsy showed a dense monomorphous dermal infiltrate of small mature lymphocytes that exhibited the immunocytochemical phenotype CD5 and CD20. A blood film showed smear cells and a CLL immunophenotype (CD5 and CD23; FMC7 was unusually positive). The surface immunoglobulins were of kappa type. A bone marrow examination also showed infiltration by abnormal lymphocytes, confirming the diagnosis of B-cell CLL.

Since 1988 he has undergone several surgical procedures to excise two basal and one squamous cell carcinomas from his scalp and to alleviate obstructed tear ducts, and a septoplasty for nasal obstruction. All specimens showed heavy infiltration with CLL cells. Radiotherapy to the tear ducts and nose and pulse tuneable dye laser treatment of the skin lesions were unsuccessful. He has developed a chronic peripheral neuropathy and has had two episodes of opportunistic infection since 1988 (*Legionella* pneumonia and facial cellulitis). He has consistently declined chemotherapy despite clinical (lymphadenopathy) and haematological evidence of progression of the CLL (in 1999, his haemoglobin was 10 g dL^{-1}, white cell count $51{\cdot}1 \times 10^9$ L^{-1}, lymphocytes $30–40 \times 10^9$ L^{-1}, platelet count 86×10^9 L^{-1}). The only prophylactic treatments acceptable to our patient have included daily oral amoxycillin, yearly gamma-globulin infusion and biannual influenza immunization.

In 1999 he presented with further cutaneous CLL infiltration affecting his toes and trunk. There was an extensive, cool, dusky, perniotic plaque over the abdomen and nose and discrete patches of infiltrate scattered on the arms and upper back. The patient had noted an improvement of these signs following exposure to natural sunlight, and the suggestion of broad-band ultraviolet (UV) B therapy was accepted.

Following 24 treatments, a marked resolution of the cutaneous deposits was noted (Fig. 1a,b). This was accompanied by an improvement in the haematological indices (haemoglobin $12{\cdot}4$ g dL^{-1}, platelet count 148×10^9 L^{-1}, with no change in the lymphocytosis of 51×10^9 L^{-1}) and resolution of the perniotic plaque over his abdomen. However, within 6 months the deposits had recurred and he has recently received a further successful course of UVB.

Leukaemia cutis occurs in up to 25% of patients with CLL[1] if one takes account of nonspecific findings including

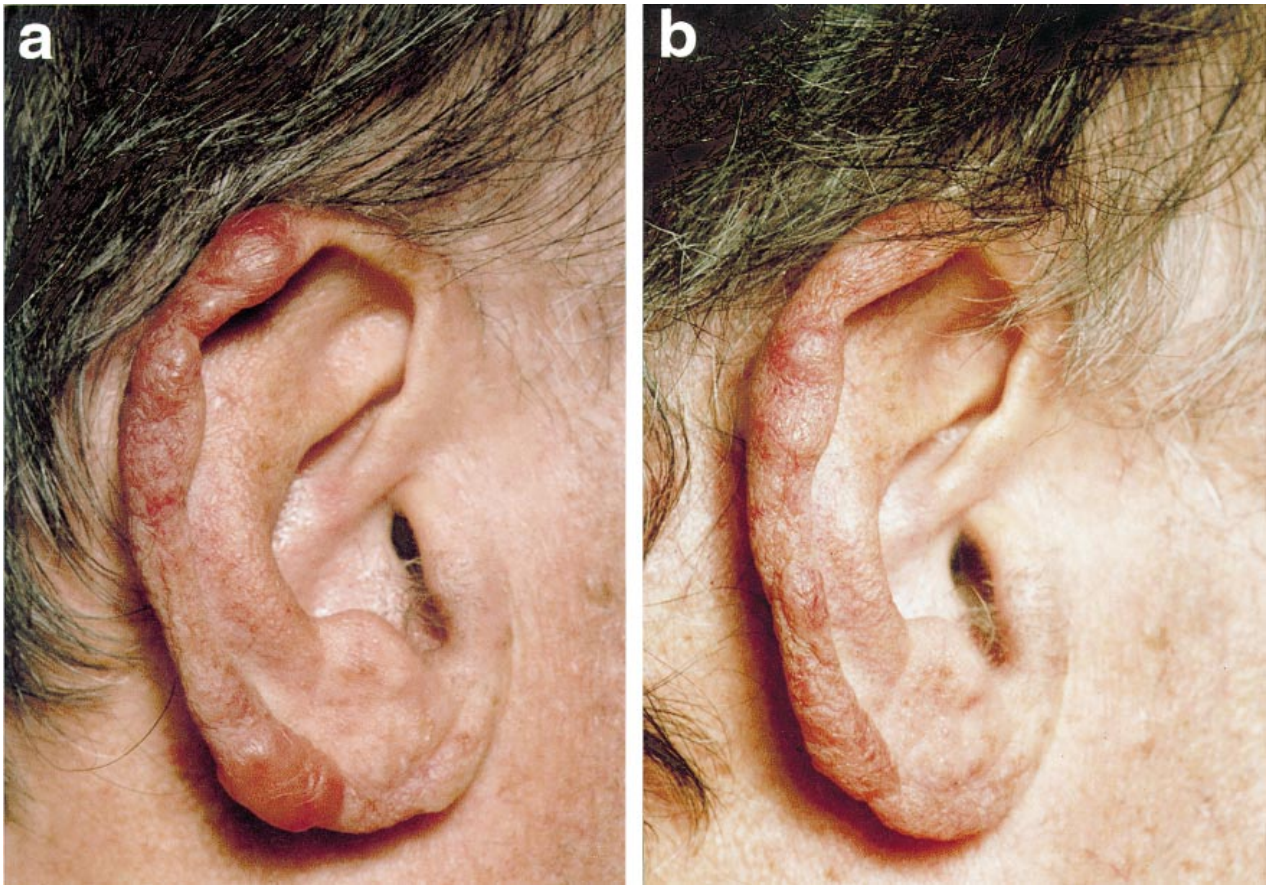

Figure 1. Leukaemic deposits (a) before and (b) after ultraviolet B phototherapy.

pruritus, purpura, urticaria and erythroderma. Specific deposits of CLL may appear as macules, plaques, papules, nodules, ulcers and even bullous lesions. Lesions are typically seen on the face, particularly the ears. The perniotic plaque experienced in this case may be a result of cells 'sludging' in cutaneous vessels. Perniosis has been reported in three previous cases and possibly as an association of a preleukaemic state.[2] Cutaneous lesions are uncommonly the presenting features of a systemic leukaemia.[3,4] Su *et al.*[3] suggest that the appearance of skin signs in systemic leukaemia carries a poor prognosis, although this is not the experience of all authors;[5] our patient appears to demonstrate a particularly indolent disease process despite the original cutaneous presentation.

Patients with CLL have a higher incidence of other neoplasms than the normal population. The appearance of other cutaneous malignancies in our patient might be expected because of prolonged immunosuppression. Infiltration of these lesions by leukaemic cells has been reported before[6,7] and may represent localized areas of host immune response.

Treatment of systemic CLL is with chlorambucil and other agents such as cyclophosphamide and fludarabine. Non-specific cutaneous signs have been successfully treated with prednisolone, psoralen plus UVA (PUVA) and extracorporeal photopheresis; specific deposits usually respond to conventional radiotherapy or electron beam irradiation. There have been no previous reports of the use of UVB phototherapy in CLL. It is a more accessible, cheaper and probably safer treatment modality than radiotherapy and perhaps could be utilized more often in a manner analogous to PUVA in the control of symptoms and signs of cutaneous T-cell lymphoma. The mode of action is not understood but it may involve alteration of the cutaneous lymphokine profile and migration of lymphocytes from the skin to the blood. There is no ready explanation for the haematological response in our patient, but it may be similar to the phenomenon seen after treatment with systemic corticosteroids where there is a redistribution of lymphocytes from the tissues and marrow to the blood.

Department of Dermatology,
Chelsea and Westminster Hospital,
Imperial College School of Medicine,
London SW10 9NH,
U.K.
W.M.Porter
R.U.Sidwell
D.Catovsky*
C.B.Bunker
**Royal Marsden Hospital,*
London SW3 6JJ,
U.K.

References

1 Greenwood R, Barker DJ, Tring FC *et al.* Clinical and immunohistological characterization of cutaneous lesions in chronic lymphatic leukaemia. *Br J Dermatol* 1985; **113**: 447–53.

2 Marks R, Lim CC, Borrie PF. A perniotic syndrome with monocytosis and neutropenia – a possible association with a preleukaemic state. *Br J Dermatol* 1969; **81**: 327–32.

3 Su WPD, Buechner SA, Li C-Y. Clinicopathologic correlations in leukemia cutis. *J Am Acad Dermatol* 1984; **11**: 121–8.

4 Schmid-Wendtner MH, Sander C, Volkenandt M *et al.* Unusual manifestations of B-cell disorders. Case 2: chronic lymphatic leukaemia presenting with cutaneous lesions. *J Clin Oncol* 1999; **17**: 1084–5.

5 Cerroni L, Zenahlik P, Hofler G *et al.* Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. *Am J Surg Pathol* 1996; **20**: 1000–10.

6 Dargent JL, Kornreich A, Andre L *et al.* Cutaneous infiltrate of chronic lymphocytic leukemia surrounding a primary squamous cell carcinoma of the skin. Report of an additional case and reflection on its pathogenesis. *J Cutan Pathol* 1998; **25**: 479–80.

7 Smoller BR, Warnke RA. Cutaneous infiltrate of chronic lymphocytic leukemia and relationship to primary cutaneous epithelial neoplasms. *J Cutan Pathol* 1998; **25**: 160–4.

Scarring molluscum contagiosum in patients with severe atopic dermatitis: report of two cases

SIR, Molluscum contagiosum virus is a member of the poxvirus family and has two subtypes. Both produce clinically identical disease exclusively in humans. Infection is common and produces benign, self-limiting lesions over the skin and mucous membranes, mainly in children, sexually active adults and immunocompromised individuals.[1] Classically, molluscum contagiosum is considered to produce little or no dermal inflammatory response, and papules usually resolve within months without scarring.[1] We report two patients with atopic dermatitis and widespread molluscum contagiosum infection that resolved leaving extensive pitted scarring.

Patient 1. An 18-year-old woman with a long history of severe atopic dermatitis had developed widespread, marked molluscum contagiosum at the age of 10 years, confirmed on biopsy. This persisted and increased in severity such that she was referred for immunological assessment at age 12 years. However, her lymphocyte subsets were normal and no immune defect was found. Management of her atopic disease had consisted mainly of moderately potent topical steroids as well as a short course each of ultraviolet (UV) B and psoralen plus UVA therapy. By the age of 16 years her mollusca had begun to resolve but were leaving numerous disfiguring scars (Fig. 1a).

Patient 2. A 34-year-old man with a near life-long history of atopic dermatitis presented with widespread mollusca. His past treatment had included a 1-year trial each of cyclosporin (8 years before presentation) and topical 0·1% tacrolimus ointment (6 months before presentation) but disease had recurred within weeks of stopping treatment. At the time of development of molluscum contagiosum infection he was using moderately potent topical steroids only. His viral lesions persisted for some 9 months, most then clearing to leave pitted scars (Fig. 1b).

Molluscum contagiosum is considered to produce little or no dermal inflammatory response. In fact, inflammatory changes may be seen histologically and are dependent on the evolutionary stage of the lesion, with some authors noting an

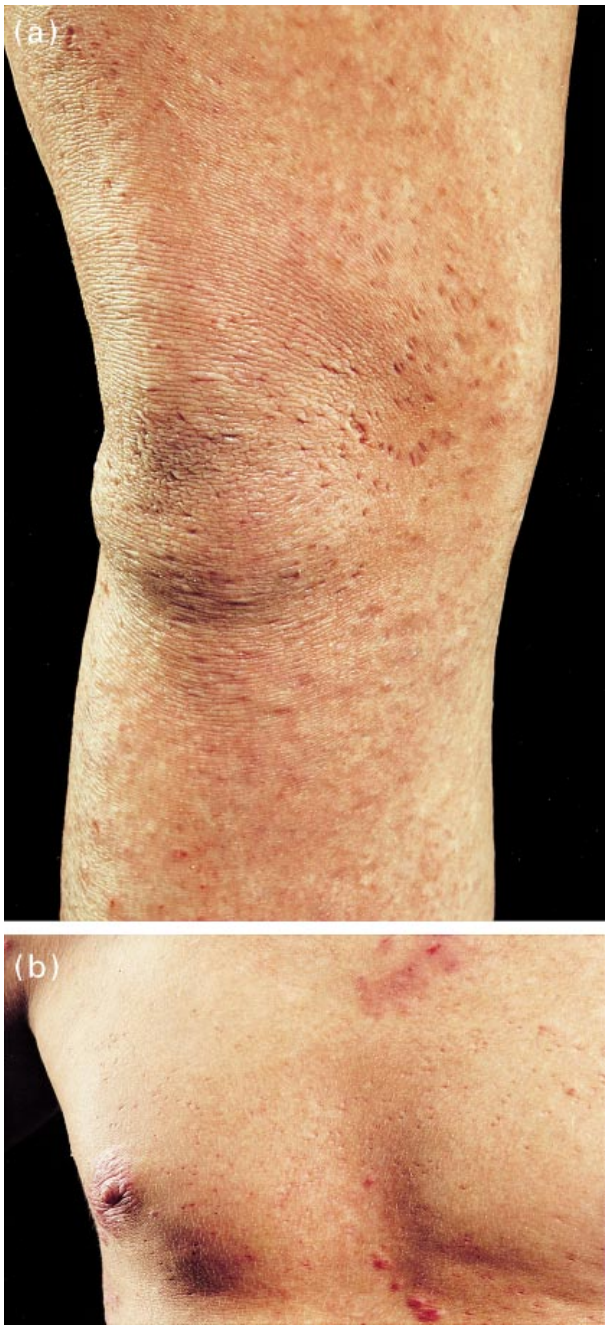

Figure 1. Pitted scarring over (a) the knee of patient 1 and (b) the chest of patient 2.

initial lymphocyte-mediated rejection pattern around tumours[2] and others on occasions describing a marked granulomatous, foreign body-type reaction which is postulated to be secondary to discharge of crater contents into the dermis, as seen in rupture of an epidermoid cyst.[3] It is recognized that patients with atopic dermatitis are more prone to molluscum contagiosum infection and can develop eczematous areas around lesions. Although this might produce occasional localized scars it would not explain the widespread monomorphic scarring seen in our patients. We have failed to find any reports of such widespread scarring induced by molluscum infection. As the two patients had severe atopic dermatitis, the disease or its treatment might well have been implicated in the scarring process. Whether the molluscum lesions in these two patients might have undergone more profound inflammatory changes during resolution is not clear.

Numerous forms of therapy have been tried for molluscum contagiosum. Physical methods are well documented and have more recently included carbon dioxide laser[4] and electron beam therapy.[5] A recent study has compared phenol ablation with simple physical expression, finding no significant difference between the two with regard to resolution of lesions but showing that phenol was significantly more likely to cause scarring.[6] Similarly, numerous drugs have been used with varying degrees of success. Cidofovir, a potent nucleotide analogue with broad-spectrum anti-DNA viral activity, was initially noted to have an apparent therapeutic effect against mollusum contagiosum when given systemically for cytomegalovirus retinitis in human immunodeficiency virus-positive patients.[7] Topical cidofovir also seemed efficacious and well tolerated,[7,8] and such administration avoids its potentially serious nephrotoxicity. However, larger controlled trials are needed before its widespread use can be recommended. In addition, it is currently costly. Similarly, the benefit of interferon-alfa in molluscum contagiosum is unclear. It has been tried both intralesionally and systemically[9] but in small numbers of patients only, and its effects are not consistent. The effects of nitric oxide have been examined in a double-blind trial of acidified nitrate cream (a nitric oxide liberator) vs. placebo:[10] a 75% cure rate was found in the active group, compared with 21% in the control group. Skin staining and irritation were frequent side-effects, although these did not stop its use. More recently, imiquimod 5% cream used in an open trial achieved a total clearance rate of 53% in 15 patients with mollusca, again apparently with few side-effects (most often erythema).[11]

With the increase in the immunocompromised population and the likely increased use of potent topical immunosuppressants such as tacrolimus in various cutaneous disorders, mollusca will probably be seen even more frequently. Our report indicates that molluscum contagiosum can leave widespread disfiguring scarring, and may point to a need for more vigorous treatment. Further clinical studies and financial considerations will determine which, if any, of the more recently reported treatments will become established.

Department of Dermatology, H.S.Ghura
Leicester Royal Infirmary, R.D.R.Camp
Infirmary Square,
Leicester LE1 5WW, U.K.

References

1 Sterling JC, Kurtz JB. Viral infections. In: *Textbook of Dermatology* (Champion RH, Burton JL, Burns DA, Breathnach SM. eds), 6th edn, Vol. 2, Oxford: Blackwell Science. 1998: 995–1095.
2 Steffen C, Markman J. Spontaneous disappearance of molluscum contagiosum. *Arch Dermatol* 1980; **116**: 923–4.
3 Henao M, Freeman RG. Inflammatory molluscum contagiosum. *Arch Dermatol* 1964; **90**: 470–82.
4 Friedman M. Keloid scars as a result of CO_2 laser for molluscum contagiosum infection. *Obstet Gynecol* 1987; **70**: 394–6.
5 Scolaro MJ, Gordon P. Electron beam therapy for AIDS-related molluscum contagiosum lesions: preliminary experience. *Radiology* 1999; **210**: 479–82.
6 Weller R, O'Callaghan CJ, MacSween RM, White MI. Scarring in molluscum contagiosum: comparison of physical expression and phenol ablation. *Br Med J* 1999; **319**: 1540.
7 Meadows KP, Tyring SK, Pavia AT, Rallis TM. Resolution of recalcitrant molluscum contagiosum lesions in HIV-infected patients treated with cidofovir. *Arch Dermatol* 1997; **133**: 987–90.
8 Davies EG, Thrasher A, Lacey K, Harper J. Topical cidofovir for severe molluscum contagiosum (letter). *Lancet* 1999; **353**: 2042.
9 Hourihane J, Hodges E, Smith J *et al.* Interferon alpha treatment of molluscum contagiosum in immunodeficiency. *Arch Dis Child* 1999; **80**: 77–9.
10 Ormerod AD, White MI, Shah SAA, Benjamin N. Molluscum contagiosum effectively treated with a topical acidified nitrite, nitric oxide liberating cream. *Br J Dermatol* 1999; **141**: 1051–3.
11 Hengge UR, Esser S, Schultewolter T *et al.* Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol* 2000; **143**: 1026–31.

Unregulated use of clobetasol propionate

Sir, Imported superpotent topical steroids are sold for use as skin-lightening agents at certain street markets in London. We describe a patient who developed striae and adrenal suppression following the purchase and inappropriate use of clobetasol propionate.

A 46-year-old Afro-Caribbean woman had a 3-month history of a hyperpigmented patch on her left forearm, and was prescribed topical beclomethasone dipropionate (Propaderm®; Glaxo Wellcome, Uxbridge, U.K.) by her general practitioner for presumed eczema. As the hyperpigmentation did not resolve, she purchased an ointment called Movate® at a local market selling unlicensed products, seemingly imported from Italy. The tube was labelled as 0·05% clobetasol propionate and the cream was described as 'anti-inflammatory, antiallergic, antipruritic' and particularly indicated in the 'treatment of the most resistant dermatoses'. She was not taking any other medications at that time.

The patient applied in total 30 g Movate ointment to the plaque, and began to notice the development of striae in the axillae and inner upper arms, which were progressive. At presentation to our clinic, the initial plaque had cleared but there

was residual skin atrophy and telangiectasia at this site. She was otherwise well, blood pressure was normal and she did not demonstrate any symptoms or signs of adrenal dysfunction.

Renal indices and serum electrolytes were normal. Urine dipstick for glucose was negative. A 24-h urinary steroid profile showed a marked decrease in steroid metabolites, indicating significant adrenal suppression. The level of total cortisol metabolites (sum of tetrahydrocortisone, tetrahydrocortisols, cortolones and cortols) was more reduced than that of the major androgen metabolites (androsterone plus aetiocholanolone). These represented 3·2% and 23·4% of normal mean levels, at 150 μg 24 h^{-1} (normal, mean ± SD, 4750 ± 1690) and 400 μg 24 h^{-1} (normal 1710 ± 1000), respectively. She did not return for follow-up and so we were unable to repeat this test to ensure that levels had normalized.

Clobetasol propionate is a superpotent topical steroid licensed since 1973 for the treatment of skin disease. Since then, the indications for prescribing such a strong topical preparation have been modified because of potential side-effects. We wish to draw attention to the increasingly common use of potent steroids among the African and Afro-Caribbean community as skin-lightening agents. Clobetasol propionate causes local vasoconstriction[1] which reaches a maximum a number of hours after topical application. This can give the impression of an immediate reduction in pigmentation, which encourages the patient to persevere in its use. Certainly there is a genuine lessening of pigmentation over the first days of use. Thereafter, however, unacceptable local side-effects may occur, often on the face, in particular an inflammatory perioral acne. This is the first report of prescription-only steroids being available 'over the counter' in the U.K. for use as skin-lightening agents, although their use in Africa is more common.

Local cutaneous adverse effects are most commonly seen with prolonged treatment (> 3 weeks), particularly on areas of thin skin such as the face and flexures, or even when less potent steroids are used under occlusion.[2] Adrenal suppression following application of potent topical steroids may not be well recognized, despite being reported in the medical literature for over 20 years.[3,4] The exact dose causing adrenal suppression varies with the individual, but as little as 2 g cream daily or 7·5 g weekly (half a small tube) has been shown to cause significant depression of the hypothalamic–pituitary–adrenal (HPA) axis.[5,6] The effects are usually subclinical, and laboratory values normalize when application of the steroid is stopped. However, patients may require replacement therapy during periods of stress such as infection or surgery.[5] With prolonged use of superpotent topical steroids, signs of exogenous steroid excess may occur.[7] In one case, a patient using topical 0·05% clobetasol propionate at a mean dose of 250 g monthly for a 5-year period developed bone demineralization complicated by avascular necrosis of the hips and vertebral compression.[8] Individual characteristics such as lean body mass, degree of adiposity, liver and renal function and absorption characteristics of the skin (increase in inflammatory skin lesions due to vasodilatation) influence the effect of the topical preparation. Previous authors have assessed the HPA axis by measuring early morning plasma cortisol levels, 24-h urinary free cortisol and 17-ketogenic steroids,[9] or by performing synacthen,[10] metyrapone[5] or insulin stress tests.[11] With the advent of newer more detailed urinary tests measuring a spectrum of steroid metabolites, testing of a 24-h urine collection can be performed as an out-patient. This is simple, and accurately reflects adrenal function.[12]

Superpotent topical steroids such as clobetasol propionate have specific indications in dermatology and, when used appropriately, are excellent tools that can obviate the necessity for systemic therapy. Their misuse or inappropriate use can result in irreversible cutaneous stigmata and occasionally adrenal suppression, which have medicolegal implications. It is worrying that prescription-only medications can be made available by non-medical personnel, and we have notified the relevant authority (Medicines Control Agency, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, U.K.).

Departments of Dermatology and F.M.Keane
**Clinical Biochemistry,* S.E.Munn
King's College Hospital, N.F.Taylor*
Denmark Hill, A.W.P.du Vivier
London SE5 9RS, U.K.

References

1 McKenzie AW, Stoughton RB. Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 1962; **86**: 608–10.
2 Harris DWS, Hunter JAA. The use and abuse of 0·05% clobetasol propionate in dermatology. *Dermatol Ther I* 1988; **6**: 643–7.
3 Staughton RCD, August PJ. Cushing's syndrome and pituitary adrenal suppression due to clobetasol propionate. *Br Med J* 1975; **ii**: 419–21.
4 Otley CC, Sober A. Over-the-counter clobetasol propionate (letter). *Arch Dermatol* 1994; **130**: 121.
5 Ohman EM, Rogers S, Meenan FO *et al.* Adrenal suppression following low dose topical clobetasol propionate. *J R Soc Med* 1987; **80**: 422–3.
6 Anonymous. Clobetasol propionate (Temovate by Glaxo). *Drug Newslett* 1986; **5**: 24.
7 Lawlor F, Ramabala K. Iatrogenic Cushing's syndrome – a cautionary tale. *Clin Exp Dermatol* 1984; **9**: 286–9.
8 Hogan DJ, Sibley JT, Lane PR. Avascular necrosis of the hips following long-term use of clobetasol propionate. *J Am Acad Dermatol* 1986; **14**: 515–17.
9 Katz HI, Hein NT, Prawer SE *et al.* Superpotent topical steroid treatment of psoriasis vulgaris – clinical efficacy and adrenal function. *J Am Acad Dermatol* 1987; **16**: 804–11.
10 Allenby CF, Main RA, Marsden RA, Sparkes CG. Effect on adrenal function of topically applied clobetasol propionate (Dermovate). *Br Med J* 1975; **iv**: 619–21.
11 Carruthers JA, August PJ, Staughton RCD. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *Br Med J* 1975; **iv**: 203–4.
12 Honour JW. Steroid profiling. *Ann Clin Biochem* 1997; **34**: 32–44.

Carbon dioxide laser for removal of multiple cutaneous neurofibromas

Sir, Neurofibromatosis 1 (NF1) patients perceive cosmetic disfigurement as the major clinical problem. In almost every

Table 1. Impact of carbon dioxide laser treatment of cutaneous neurofibromas: analysis of a satisfaction questionnaire

Items of concern	No. of patients improved	Mean level of improvement
Symptoms (pruritus, pain...)	9/11	Good
Everyday activity (sleep, work...)	5/10	Poor
Summer activities (going out in the sun, swimming, choice of clothes)	8/10	Poor
Social activity (going out, making friends...)	9/11	Good
Sexual activity	8/11	Good
Despair (feel lack of hope, worry about long-term effects...)	10/10	Good
Embarrassment (worry about what others think; worry about appearance...)	9/11	Poor

instance, this disfigurement derives from the growth of hundreds of cutaneous neurofibromas.[1] Carbon dioxide (CO_2) laser vaporization seems to be very helpful for patients with large numbers of small- or medium-sized cutaneous neurofibromas.[2–5]

Each of our patients had a 1-h procedure under general anaesthesia treating the anterior trunk by removing more than a hundred neurofibromas. The laser surgery was performed by one of us (CM) with a CO_2 laser Sonics Illumina 740 and a Porta Plume Safe 602 smoke evacuation system. Only cutaneous neurofibromas of < 1 cm in diameter were removed. The beam was continuous wave. For the sessile cutaneous neurofibromas, the CO_2 laser was used slightly defocused (spot size 2–3 mm diameter) applying about 20–30 W power. The portion above the skin level was vaporized, then the skin was squeezed on either side of the tumour allowing the subcutaneous portion to be vaporized as it protruded through the skin defect. For the subcutaneous neurofibromas, a focused beam opened the skin over the mass. Pinching or squeezing between the index finger and the thumb forced the mass through the skin defect where it could be vaporized under direct vision. Dressings with sulphadiazine ointment were used as postoperative care.

Photographs of the anterior trunk were performed before, immediately after and 3 months after the procedure. A panel of three dermatologists who had not been involved in the management of the patients evaluated the cosmetic results of the procedures, scoring the photographs of the patients using an analogue scale of 10 cm (0 = bad result; 10 = excellent result). Each patient reviewed his or her own photographs using the same scale.

A satisfaction questionnaire was sent to each patient 3 months after the procedure to measure the impact of the CO_2 laser treatment from their point of view. Questions explored the impact of this treatment on the psychosocial domain and activities of patients. Each question was assigned a five-point scale (very slight or no improvement, little, moderate, good, or excellent improvement).

Thirteen patients with NF1 (nine males and four females) were included in our study from 1995 to 1997. Their mean age was 38 ± 16 years. Eleven questionnaires were returned. Photographs of 12 patients were available for analysis.

The mean time for healing was 4 ± 1 weeks. No complication occurred during or after the procedure. Two of 11 patients reported moderate pain and 9/11 reported moderate pruritus during healing. All 11 patients who answered the questionnaire had previously experienced surgical excision of cutaneous neurofibromas. Seven patients judged that the resulting scars were as or more acceptable than those obtained with surgical excision of similar neurofibromas. The four remaining patients judged their scars inferior to surgical excision. Eight of 11 patients were satisfied and wished to undergo additional procedures.

Using the analogue scale to judge the cosmetic results on photographs of 12 patients, the three practitioners gave a mark of 6·25 ± 1·5 to the improvement. Patients gave a mark of 8·25 ± 0·75. For both the patients and the assessment panel the procedure improved the cosmetic appearance (Fig. 1). Table 1 summarizes the impact of CO_2 laser on patients.

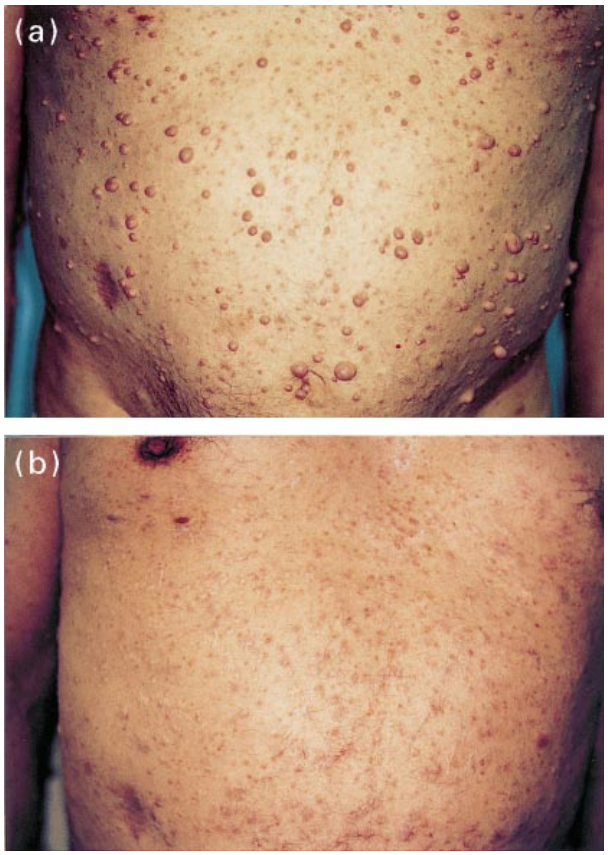

Figure 1. (a) A 52-year-old patient before the carbon dioxide laser procedure for removal of cutaneous neurofibromas; (b) 3 months after procedure.

The CO_2 laser procedure under general anaesthesia is a simple technique allowing destruction of hundreds of cutaneous neurofibromas with a minimal morbidity. This procedure results in a flat, smooth depigmented scar that might be judged to be of mediocre quality; nevertheless, most NF1 patients included in our study who had previously had surgical excision and considered the CO_2 laser scars as acceptable as those obtained with surgery, were sufficiently pleased with these results that most of them wished to undergo additional procedures. Interestingly, the judgement of critical observers, a panel of dermatologists, gave cosmetic benefit inferior scores compared with those of the patients. Patients undoubtedly preferred these mediocre scars to the initial lesions. Destruction by CO_2 laser also improved symptoms linked to the presence of neurofibromas (pruritus and pain) and patients reported a good improvement in their social and sexual life. The despair, i.e. the absence of hope linked to the consciousness of carrying an evolving disease, was reduced by the radical extirpation of hundreds of neurofibromas.

Departments of Dermatology and J-C.MORENO
**Plastic and Reconstructive Surgery,* C.MATHORET
Hôpital Henri-Mondor (AP-HP), L.LANTIERI*
Paris XII University, J.ZELLER
F-94010 Créteil cedex, France. J.REVUZ
Correspondence: Dr Pierre Wolkenstein P.WOLKENSTEIN
E-mail: wolk@univ-paris12.fr

References

1 Ablon J. Gender response to neurofibromatosis 1. *Soc Sci Med* 1996; **42**: 99–109.
2 Roenigk RK, Ratz JL. CO_2 laser treatment of cutaneous neurofibromas. *J Dermatol Surg Oncol* 1987; **13**: 187–90.
3 Becker Dw Jr. Use of the carbon dioxide laser in treating multiple cutaneous neurofibromas. *Ann Plast Surg* 1991; **26**: 582–6.
4 Katalinic D. Laser surgery of neurofibromatosis 1 (NF1). *J Clin Laser Med Surg* 1992; **10**: 185–92.
5 Bromley GS, Sherman JE, Goulian D. Neurofibromatosis – distribution of lesions and surgical treatment. *Ann Plast Surg* 1982; **8**: 272–6.

Oral terbinafine treatment for toenail onychomycosis

SIR, The letter from Molin *et al.*[1] is a welcome addition to our long-term perspective on nail fungal therapy and it is creditable that they have kept track of so many of their onychomycosis patients. However, there is a tendency for doctors and pharmaceutical companies to present data in an optimistic light, such that expectations can outstrip reality. Epstein[2] employed a very useful measure of success, that would be understood by all patients: whether the nail is without any disease at the end of treatment. Using the questionnaire data, this alone would reduce the number of long-term successes in Molin's report to 30 after the standard course of treatment. When this is expressed as a percentage, there is a choice of denominator: those who responded to the questionnaire or the number enlisted for treatment. The results are 25·6% and 31%, respectively; 25·6% is considerably less than the 78% classified as 'responders'. The gap is mainly due to three factors: (1) the choice of denominator; (2) where 'response' means improvement but not resolution; and (3) where there may be an abnormal nail to start with before the fungal infection.

This divergence of results between two ways of looking at the same data is not rare and it would be useful if it were standard statistical and clinical practice to try to have a section in any report that took the opposing view rather than looking to support an angle. Of course, the other point that arises from only a 25·6% cure rate is perhaps it is time for a new treatment for onychomycosis?

Bristol Dermatology Centre, D.DE BERKER
Bristol Royal Infirmary,
Bristol BS2 8HW, U.K.
E-mail: deberker@nails.u-net.com

References

1 Molin L, Tarstedt M, Engman C. Oral terbinafine treatment for toenail onychomycosis: follow-up after 5–6 years (Letter). *Br J Dermatol* 2000; **143**: 682–3.
2 Epstein E. How often does oral treatment of toenail onychomycosis produce a disease-free nail? An analysis of published data. *Arch Dermatol* 1998; **134**: 1551–4.

Oral terbinafine treatment for toenail onychomycosis: reply from authors

SIR, Our report[1] on the long-term effect of terbinafine treatment on mycotic toenail infections has been criticized from a statistical and evaluation point of view. In responding, it is important to state that this study was performed without support of any kind from any pharmaceutical company. The patients involved in this study were individuals who had suffered from their mycotic toenail infections for many years, reporting considerable impairment of their quality of life by thickening of the nails which made the use of proper shoes difficult, due to pain and/or odour. They were treated during the period immediately after the registration of terbinafine in Sweden. The criteria for initiating treatment were a widespread infection and different complaints, not only cosmetic, due to the nail infection. Thus, in some ways, they were a selected patient population.

We, of course, agree that there is always a need for criteria in evaluating the results of various treatments in all fields of medicine. However, from the patient's point of view, the importance is not only to have good-looking nails but to be free from all discomfort irrespective of residual discolourations. How many toenails are really completely free of any dystrophic or colour disfiguration in adults? We therefore used the term 'response' and not 'without any sign of disease'. Of course the ideal patients are those who have been recorded as having toenails 'without any sign of disease' already before being infected, but where do you find them?

Therefore, we still maintain that the study resulted in a therapeutic response to the treatment with terbinafine in three out of four cases after long-term follow-up in patients who had suffered from mycotic infections of the toenails for years before treatment. That is the relevant fact for the patients. Other antimycotic drugs given by mouth have been available on the market since the introduction of terbinafine. However, none proved to be so much better. Even with a response in three out of four cases there is, of course, need for better treatment for onychomycosis.

Department of Dermatology, L.MOLIN
Örebro Medical Centre Hospital, M.TARSTEDT
Örebro, Sweden C.ENGMAN
Correspondence:
E-mail: lars.molin@orebroll.se

Reference

1 Molin L, Tarstedt M, Engman C. Oral terbinafine treatment for toenail onychomycosis: follow-up after 5–6 years (Letter). *Br J Dermatol* 2000; **143**: 682–3.

Book Review

Handbook of Paediatric Dermatology J.VERBOV (2000). London: Martin Dunitz. ISBN 1-85317-888-8, 224 pages. Price £39.95.

In these days of evidence-based practice, a book based unashamedly on the authors' own enormous experience and opinions is like a breath of fresh air.

The layout of the book is familiar from Verbov's *Essential Paediatric Dermatology* (Clinical PTCSS, 1988) with chapters including the newborn, eczema, infections, erythematosquamous eruptions, hair and nails, naevi and nodules, connective tissue disorders, vascular disorders and drug eruptions, genodermatoses, bullous disorders and mastocytoses, acne, trauma, light and pigmentation disorders. A section on the mouth has been added and the text extended. The familiarity of many excellent photographs from the earlier book in no way detracts from their quality.

The format is ideal for the target readership: trainee dermatologists, paediatricians, GPs, clinical medical officers, senior medical students and nurses. It is a good book to browse through or dip into to extend or consolidate one's knowledge. It is less useful when seeking an unknown diagnosis, because the organisation is sometimes based on pathology, sometimes anatomy and sometimes age, without cross-referencing. Thus, a search for causes of alopecia in the section on hair will miss those in the section on infection (e.g. tinea). Nail dystrophies are not confined to the section on nails, but scattered among chapters on infections, genetic disorders and bullous diseases.

The subject matter usefully reflects the workload of a general paediatric dermatologist. Illustrations of several different presentations of atopic dermatitis, psoriasis and scabies are most helpful. Many of the important rare disorders are mentioned and well-illustrated but there are significant gaps. Epidermolysis bullosa falls inadequately between chapters on the newborn and on bullous disorders, and Herlitz junctional EB (not illustrated) is mentioned in only one sentence. Lichen planus is not recognisable from the single illustration, and plane warts (omitted) might well be misdiagnosed as sarcoidosis by anyone seeking a visual match in this book. Doctors puzzling over paediatric inpatients will hunt in vain for pictures of skin lesions of acute GVHD and Stevens–Johnson syndrome. Those requiring a more comprehensive text will find Higgins and du Vivier's *Skin Disease in Childhood and Adolescence* preferable but more expensive, at £52.50.

These are however minor criticisms and reading this book is almost as good as a teaching clinic with Professor Verbov, hearing him explain to parents, trainees and colleagues in his fatherly manner. The patients are his own, and so are the opinions. His great breadth of experience, enthusiasm and irrepressible urge to teach combine to produce a book to treasure.

CELIA MOSS

Erratum

Russell-Jones R. Immunotyping of Sézary cells. *Br J Dermatol* 2000; **144**: 2–3.

In this editorial comment, a new reference 1 was inserted into the reference list, but the reference numbers were not adjusted in the text. Therefore, each reference number in the text corresponds to the following number in the list, and the citation for reference 1 should have appeared in the first line of the first column.

The publisher apologises for any confusion caused.