Is Kinky-Hair Disease a Misnomer for Menkes Syndrome?

Although we had the satisfaction of correctly diagnosing "Fragile Hair and Seizures in a Child" in your March issue, and were interested to read about it, we would like to add a little further information about the hair microscopy findings in Menkes syndrome. In his original article in 1962, John Menkes described a sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration in 5 children. In only 2 of the children was the hair kinky, although in all of them it was sparse and wiry.

It was Danks in Australia from 1972 onward who carried out most of the work on Menkes syndrome. With the help of research into the wool of sheep deficient in copper, he and his colleagues established the presence of decreased levels of copper and ceruloplasmin (the copper transport protein) in the serum of children with Menkes syndrome, and low copper content in their hair. There is reduced activity of copper-containing enzymes, eg, dopamine β-hydroxylase, tyrosinase, throughout the body. This leads to progressive psychomotor retardation in the first few months of life with drowsiness, impaired temperature regulation, and convulsions, as well as various connective tissue abnormalities including laxity of the skin and fragility of the hair with hypopigmentation of both. By 1989 Danks wrote about Menkes (steely hair) syndrome. The defective gene has been localized to chromosome Xq13 by linkage analysis and is responsible for the lack of a copper transporting adenosine triphosphatase enzyme.

Many different abnormalities of the hair shaft have been described in Menkes syndrome. There is usually normal hair at birth, but after a few months the hair becomes coarse and brittle, fractures easily, and usually becomes lighter in color. Hairs from some patients with Menkes syndrome show pili torti (strict 180° twists in alternate directions) that may give rise to unruly hair, but hairs from others show irregular twisting, sometimes loose twists all in one direction, variations in diameter, trichorrhexis nodosa, trichoclasia, and occasionally inconsistent variation in bore-mimicking monilethrix microscopically. The latter signs are all extrinsic, acquired, degenerative changes due to excessive weathering and occur in other types of twisting dystrophy, eg, dystrophic pili torti.

The kinky, rather unruly hair of pili torti, a physical sign only, may exist alone in classic or late-onset pili torti, or it may occur with other signs and point to a variety of conditions, Menkes syndrome being one. Others are Björnstad syndrome, pseudomonilethrix, Bazex syndrome, Crandall syndrome, hypohydrotic ectodermal dysplasia, and trichothiodystrophy. Alternatively, pili torti may not be diagnosed because excessive weathering has occurred, masking the microscopic changes.

We have looked at light and scanning electron micrographs of hair shafts from patients with Menkes syndrome. A, An SEM showing repeated twisting (pili torti) of the hair shaft (bar indicates 50 µm). B, A TEM of the periphery of a cross section of the hair shaft illustrating the multilayer cuticle (Co) overlying the cortex (Cu) (silver methenamine staining; bar indicates 1 µm). C, Detail of the junction between the cortex and cuticle; the cuticular cells possess a very electron-dense A layer (AL), a less dense exocuticle (E), and an electron-lucent endocuticle (En). Note that the fine microfibrils (F) of the cortex are surrounded by electron-dense material (silver methenamine staining; bar indicates 0.1 µm).
analysis, the silver and routinely stained sections did not show any intrinsic defect (Figure, B-C).

Despite studies looking at copper content of the affected hairs, reduction in disulfide bonds, and a proposed reduction in activity of sulfhydryl oxidase in hair, the fact remains that the hair abnormality in pili torti, whether in Menkes syndrome or not, is a congenital fixed fault of twisting dystrophy, with added acquired change due to excessive weathering. The important message should be that if pili torti is found on routine microscopy, it should be considered a physical sign, and other underlying or associated factors should be sought so that disorders such as Menkes syndrome are not missed.

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Revised Terminology in Dermatology: A Call for the New Millennium

Clinical dermatology has always been a descriptive and morphologic specialty. Our early predecessors depended on the naked eye as their instrument of description and resorted to Latin terms to label diseases of the skin. Consequently, we inherited a plethora of names of diseases with which we are still intimately involved. Although the raison d’être for our specialty is that dermatologists are morphologists, all disciplines in medicine have witnessed change, and dermatology is not an exception. To keep our specialty a scientific discipline, we must establish order in the current use of dermatological terms and refrain from using the ambiguous terminology that has become part of our specialty.

The simple rule for a revised dermatological lexicon is that clear, precise terms should be kept, and confusing or ambiguous ones changed. It is patently silly for each dermatologist to have his or her own set of terms. The great source of difficulty in classification and nomenclature lies in the fact that there are 2 distinct and unrelated systems, one based on etiology and the other on morphology. This neat statement was first proposed in 1935 by Williams when the only diagnostic tool available to us was the naked eye. Thus, many of the names that were coined at that time used polysyllabic Greek or Latin terms or their combination. Justifiable as it may be, the basis for these designations is whimsical and dependent on etiology, distribution, the affected anatomic compartment in the integument, or a combination of all of the above.

With the advent of molecular biology and modern technology, and their limitless uses in the understanding of skin disease, it is unreasonable to maintain this chaotic use of terms and definitions in our specialty; we propose a revised nomenclature based on logic. It may feel comfortable to maintain in our lexicon terms such as “peau d’orange” for mycosis fungoides and breast cancer, “furfuraceous” for the branlike scale of tinea versicolor, “honey-colored” crusts of impetigo, and so on and so forth. Yet it is also heartening to acquire words such as Kt T-cell lymphoma or like terms to reflect the level of sophistication in our growing vocabulary.

Also in this context, should modern dermatology retain terms like “hyperkeratosis follicularis et parafollicularis in cutem penetrans”? If so, then is it to impress or perhaps perplex our dermatology residents, or is it to remind us of the descriptive and morphologic nature of our specialty?

Our specialty would greatly benefit from the revision of many names of skin diseases. Just a few of numerous possible examples include:

- “Perforating elastosis” to replace “elastoma intrapapillare perforans verruciforme” and “elastosis perforans serpiginosa.”
- “Perforating hyperkeratosis” to replace “hyperkeratosis follicularis et parafollicularis in cutem penetrans.”
- “Pemphigoid gestationis” to replace “herpes gestationis.”
- “Necrobiotic papulosis” to replace “granuloma annulare” (which is neither a granuloma in the conventional meaning nor necessarily annular).
- “Reactive hemangioma” to replace “granuloma pyogenicum” (which is neither a granuloma nor pyogenic).
- “Acnitis” to replace “lupus miliaris disseminatus faciei.”
- “Cutaneous tuberculosis” to replace “lupus vulgaris” and “tuberculosis verrucosa cutis” and “scrofuloderma.”
- “Solar guttate hypomelanosis” to replace “idiopathic guttate hypomelanosis.”
- “Interdigital candidal intertrigo” to replace “erosio interdigitalis blastomycetica.”
- “Psoriasis climactericum” to replace “keratoderma climactericum.”

Some of these revised terms are already in use, and it is time to regard the old ones as obsolete.

This proposal is to shed the old and don the new. In no way is it intended to defame our great heritage, a heritage to be forever cherished. It is simply to introduce simpler, more correct nomenclature, especially in the light of the tremendous advances in modern dermatology.

It is further suggested that a task force be formed to conduct a survey for the revised names of diseases and publish a glossary of the new nomenclature. This is in line with previous attempts made by the International
League of Dermatological Societies and its Committee on Nomenclature.9

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Evaluation of Therapeutic Success of Hyperhidrosis Therapy

We read with interest the article by Karamfilov et al1 suggesting lower relapse rates of hyperhidrosis after high-dose botulinum toxin type A injections (BOTOX; Allergan Inc, Irvine, Calif; hereinafter, generically, botulinum toxin A).1 Various protocols for treating hyperhidrosis with botulinum toxin A have been issued empirically without controlled comparison of doses, dilutions, number of injections, or pharmaceutical products. Thus, any attempt to provide evidence-based information on how to optimize botulinum toxin A treatment should be welcomed. For this purpose, however, stringent study designs, accurate measurements of sweating, and uniform follow-up schedules are indispensable. Unfortunately, Karamfilov et al1 did not implement a control group receiving low-dose botulinum toxin A, which could have been easily provided by a left-vs-right comparison, with each patient being his own control.

Also, the iodine-starch test and planometry, which are helpful to visualize the active hyperhidrotic area, are not pertinent for exact quantification of sweating. In fact, positive findings on the iodine-starch test easily occur not pertinent for exact quantification of sweating. In fact, positive findings on the iodine-starch test easily occur. It is, however, the rate of sweating (amount per minute) that makes a person hyperhidrotic, and this can accurately be determined by gravimetry using blotting paper, a high precision scale, and a stopwatch.2 In 156 patients recently screened for severe axillary hyperhidrosis, the mean±SD active area as visualized by the iodine-starch test was 48.3±4.4 cm², ranging from 14.2 to 66.5 cm², which showed no correlation to actual sweat rates measured by gravimetry (52-858 mg/min). The fact that gravimetric values may vary considerably does not discredit this method but rather demonstrates the dynamics of eccrine glands in hyperhidrosis. After botulinum toxin A treatment, gravimetric sweat rates have been shown to be consistently low.2,3

Follow-up as reported by Karamfilov et al1 ranged from 5 to 15 months, but it remained unclear at what intervals patients were observed—if there was any regular follow-up schedule at all. Waiting for the patient to ask for subsequent treatment is definitely too volatile a parameter for a clinical study, especially when trying to establish measurable benefits compared with already existing protocols. Finally, but not of least importance, the safety of high-dose botulinum toxin A as proclaimed by Karamfilov et al1 is questionable; the authors failed to mention that the risk of antibody induction rises not only with treatment frequency but also particularly with higher doses.4

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The Wheal: To Be or Not to Be

Sad to say, until a dictionary of dermatology equivalent to the Oxford English Dictionary comes into being, dermatology will forever be a twigglike imposter, rather than an authentic branch of knowledge.

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It is astonishing that the current significantly different meanings of the term cutaneous elementary lesions have received so little attention in dermatology journals. But it is precisely for this reason that the renewed controversy regarding basic dermatological lesions reflected in the ARCHIVES holds great interest.1 The suggested elimination of wheal “from the list of basic terms” is worthy of comment. In our opinion, there are also reasons favoring its preservation on such a list. Dermatologists have traditionally used a specific term to describe lesions of urticaria except in French dermatology. The analysis of such a tradition may contribute to a better understanding of this controversy.3

English Tradition. Wheal is an Anglo-Saxon word. Robert Willan and Thomas Bateman turned this into a spe-
cialized dermatological term. Although they did not call it an elementary lesion, they defined the wheal as the “rounded or longitudinal elevation of the cuticle, with a white summit, but not permanent, not containing a fluid, nor tending to suppuration.”

The use of the term *wheal* certainly contributed to increasing the precision of dermatological thought and to distinguishing urticaria from other exanthems. Even though writings concerning urtication of the skin could be found in Hippocratic treatises, we cannot forget that lesions of urticaria were described as *pustules* or merely as “little elevations” before Robert Willan incorporated wheal into the dermatological lexicon.

German Tradition. Ferdinand Hebra \(^8\) was the first author to consider lesions of urticaria (*quaddeln*) elementary lesions. He defined them as “solid lesions, not project- ing greatly above the skin and with a horizontal diameter much greater than the vertical one.”

Spanish Tradition. José Olavide \(^9\) introduced and defined the Spanish words “habón” and “roncha” (as wheals), also in the 19th century. Such terms are still in use today.

French Tradition. On the contrary, French dermatology did not use any specific term to describe lesions of urticaria. Jean Darier \(^10\) described urticaria as an “erup- tion consisting of individual elements that, lacking a special name, are called urticarial plaques or papules.”

Modern Usage. The current controversy concerning the wheal in the *Archives* \(^1–4\) is therefore a consequence of the linguistic traditions described herein. The following 2 definitions can be distinguished: Definition 1: Nonmorpholog- ical (the wheal of Willan). This definition is the most widespread today. The wheal of Watt \(^1\) (“varies in size, elevated, transient”) is reminiscent of the wheal of Willan, an evanescent evolution being its fundamental characteristic. Lewis, \(^2\) like others since the beginning of the 20th century, \(^11,12\) added another nonmorphological but histolog- ical characteristic: dermal edema. Definition 2: Morphological. This definition is reminiscent of Hebra’s, \(^8\) but unlike that of the wheal of Willan, this definition has dissa- peared from usage, converging with the French tradition. This wheal has been subcategorized into 2 lesions, papule and plaque, and finally its elimination from the list of elementary lesions is suggested. \(^3,4\) The *wheal* of Hebra is no longer used, but the wheal of Willan is still in use today \(^5,6\) and will probably be retained for the next few years; changing such a deep-rooted linguistic tradition is a slow process.

The controversial point here is that the Watt definition of the wheal is an exception at the present time. It is a nonmorphological concept, unlike the rest of the definitions of elementary lesions, and is not generally accepted. \(^4\) Thus, to define the wheal we must either make a new morpho- logical definition or accept this exception. In our opinion, the advantages of conserving this word as a specialized term compensate for the exception to its definition.

To define the wheal we can also retrieve one of its forgotten aspects: dermatographism. Wheals of Willan in- cluded linear lesions, but this was later overlooked in stan- dard definitions. \(^12\) Surprisingly, this was the violent origin of the modern meaning of the word. According to the *Oxford English Dictionary*, the wheal was at first “the mark or ridge raised on the flesh by the blow of a rod or lash.” \(^13\) The Spanish word *roncha* also had the same meaning. \(^14\)

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308-nm Excimer Laser Therapy for Psoriasis

In a recent issue of the *Archives*, Asawanonda et al \(^1\) reported a dose-response study with a 308-nm excimer laser for the treatment of psoriasis. The authors cited our earlier work, \(^2\) mentioning that we “established some efficacy for excimer laser-generated 308-nm radiation in the treatment of psoriasis,” and that we concluded that psoriasis required 7 to 11 treatment sessions to clear.

Indeed, we did provide the first evidence that the 308-nm xenon chloride laser was highly effective for the treatment of psoriasis. However, our real conclusion was that this laser light was more effective than the 311-nm narrow-band UV-B (NB-UVB) treatment in psoriasis. We found that the number of treatments, the duration of the phototherapy, and, probably most importantly, the cumulative UV-B dose were much lower in the xenon chlo- ride laser–treated plaques than in the NB-UVB–treated lesions.
The stepwise increase of the UV-B doses (starting with $0.5 \times$ the minimal erythema dose) that we applied in our study was the conventionally used treatment protocol for the NB-UVB therapy of inflammatory skin diseases.\textsuperscript{3} In contrast, repeated treatment with the same dose, as used by Asawanonda et al.,\textsuperscript{1} is rather unusual; it is possible that the increased skin tolerance developing after irradiation was the reason that significant differences were not observed between the clinical efficacies of 1 or 20 treatments when the fixed low to medium UV-B doses were used.

In our patient cohort, the length of remission induced by the 308-nm excimer laser has proved surprisingly long; from the 10 patients enrolled in our previous study,\textsuperscript{2} 8 are still symptom free on their laser-treated areas after 2 years. Further investigations to optimize the 308-nm excimer laser treatment by changing the intensity and frequency of the impulses, by establishing the most appropriate starting dose, and by using fixed or increased fluences might result in improved therapeutic approaches for the treatment of UV-responsive skin diseases.

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In reply

We thank Kemény et al for their comments on our article in a recent issue of the ARCHIVES.\textsuperscript{1} We agree that the 308-nm excimer laser is a very effective tool for the treatment of psoriasis. Our subsequent unpublished studies confirm that rapid clearing can be achieved in most patients, compared with both conventional broadband and NB-UVB historical controls. We also readily acknowledge that for 6 patients, Kemény et al established the superiority of the 308-nm excimer laser over narrow-band 311-nm phototherapy for the treatment of localized psoriasis.\textsuperscript{2}

In their original report, Bónis et al\textsuperscript{2} treated psoriasis with a phototherapy approach, meaning that their treatment was started at a suberythemogenic fluence and gradually increased. The aim of such a standard approach is to provide clearing without causing erythema. For traditional phototherapy, this dose escalation makes sense because both involved and uninvolved skin are being exposed. Kemény et al further emphasize the importance of this fluence escalation in phototherapy to overcome the hindrance incurred by acclimatization.

Our recent study,\textsuperscript{1} however, had a very different design and purpose, namely, that of a dose-response investigation for the 308-nm excimer laser alone; it was not a treatment trial, nor a comparison one. The actual fluences were based on multiples of the baseline minimal erythema doses. Psoriatic plaques can tolerate higher fluences of UV radiation than uninvolved adjacent skin. Because these plaques were being selectively targeted in our dose-response investigation, we decided to adopt more of a laser-treatment approach, meaning that the excimer pulses were delivered at fixed doses with a range of fluences from suberythemogenic to supraerythemogenic. Indeed, our results showed that fluence is the single most important determining factor for clearing of psoriasis. We believe that, especially at the higher dose multiples, clearing may be able to proceed faster than tolerance can be induced, and it may not be necessary at all to increase the dose at subsequent sessions.

We agree that further studies are needed to optimize treatment with this novel therapy. We speculate that the ideal approach for localized, limited plaques may well be single or at most a few “high-dose” treatments, whereas for widespread psoriasis several “medium-dose” treatments may make more sense. In either case, the total number of treatments to clear and the cumulative dose at clearing will almost certainly be less than that obtained for traditional NB-UVB phototherapy.

We further hypothesize that when the 308-nm excimer laser treatments are selectively directed on individual psoriasis plaques, standard phototherapy style dosimetry, which takes into account treating the whole body (both involved and uninvolved skin) may not be the optimal dosing method. Under these selective conditions, one is not limited by phototoxicity of the adjacent, uninvolved skin; high enough doses may effect clearing before tolerance becomes a significant obstacle. We look forward eagerly to the possible use of excimer lasers for practical phototherapy of psoriasis and other skin disorders.

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About 1 year after this study was finished, Dr Anderson became a paid consultant for Laser Photomedix (formerly Laser Phototronics), San Diego, Calif.

VIGNETTES

Herpetic Folliculitis and Syringitis Simulating Acne Excoriée

Acne excoriée is a disease in which patients, usually young women, habitually pick or scratch ef- florescences due to preexisting adolescent acne vulgaris. Acne excoriée is considered a psychoneurotic disease, with neurotic excoriations serving as a “protective device” or an “appeal for help.” Conventional treatment for acne vulgaris is usually ineffective for acne excoriée; both dermatologists and psychiatrists should be involved in recommending adequate dermatological treatment along with psychotherapy and tranquillizers. We describe the case of a 46-year-old woman with a long-standing history of acne excoriée, confirmed by several dermatologists, that finally was unmasked as herpetic folliculitis and syringitis.

Report of a Case. A 46-year-old, white, nonatopic woman who had not suffered from severe acne vulgaris in puberty developed acneiform lesions on her face at age 25 years. Subjective symptoms like palpitation, burning, and itching made her pick and squeeze these lesions. Numerous recurrences over the next 20 years led to considerable scar formation. The “acne lesions” had resisted the acne treatment advised by several dermatologists. Because of her skin lesions, she was in deteriorating psychological condition that seemed to support a diagnosis of acne excoriée.

On admission to our clinic, the patient exhibited grouped papules, excoriations, and superficial ulcerations beside hyperpigmented and hypopigmented scars on her forehead (Figure 1), cheeks, and chin. The submental lymph nodes were slightly enlarged. Results of a blood count and serum chemistry profile were normal, and human immunodeficiency virus serology findings were negative.

When treatment for acne was again ineffective, a 5-mm punch biopsy was performed on demand of the patient. Histopathologic examination revealed a dense, dermal lymphocytic infiltrate involving the pilosebaceous units, with partial necrosis of the sebaceous glands. Follicles and eccrine ducts showed multinucleate keratinocytes with steel-gray nuclei (Figure 2). The DNA extracted from the paraffin-embedded specimen was successfully amplified by polymerase chain reaction using herpes simplex virus (HSV)—specific primers. Serological testing by enzyme-linked immunosorbent assay detected IgM and IgG antibodies to HSV.

The patient started antiviral treatment with 500 mg of valacyclovir once daily. Since beginning antiviral therapy 1 year ago, she has experienced only 2 minor episodes of herpetic infection, manifested by discrete erythematous papules in the old scar on her forehead and associated with mild pain and itching of a few days’ duration.

Comment. Over a period of 20 years, our patient suffered from recurrent episodes of acneiform lesions on the face clinically resembling acne excoriée. Herpesvirus folliculitis and syringitis was diagnosed only by histopathologic examination. The diagnosis of HSV infection was confirmed by polymerase chain reaction amplification of HSV DNA, by detection of HSV-specific antibodies using enzyme-linked immunosorbent assay, and by the positive response to antiviral therapy with valacyclovir.

In herpesvirus infection of the skin, the histopathologic changes are often limited to the epidermis. Remarkably, the involvement of the follicular epithelia (her-
petic folliculitis)\textsuperscript{2-5} and the sebaceous and eccrine structures (herpetic syringitis)\textsuperscript{4-5} is only rarely reported in the literature. The main clinical differential diagnosis of herpetic folliculitis and syringitis is eczema herpeticum, which usually occurs in patients with preexisting skin disease, eg, Darier-White disease or keratosis follicularis. In conclusion, herpetic folliculitis and syringitis should be considered relevant differential diagnoses in patients with acneiform lesions that fail to respond to conventional acne treatment.

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Birt-Hogg-Dube Syndrome: Treatment of Cutaneous Manifestations With Laser Skin Resurfacing

Birt-Hogg-Dube syndrome (BHDS) is an autosomal dominant disorder characterized by multiple fibrofolliculomas, trichodiscomas, and acrochords. Some patients also exhibit multiple hidradenomas. Extracutaneous manifestations are rare and include renal cell carcinoma, colonic polyps, and recurrent spontaneous pneumothorax.

Treatment for the disfiguring skin lesions is limited. We describe a case of BHDS treated successfully with carbon dioxide and Er:YAG laser skin resurfacing.

Report of a Case. A 46-year-old man presented to the dermatology department with complaints of multiple, slow-growing lesions of cosmetic concern on the forehead, cheeks, and nose. The lesions appeared as ivory-colored, slightly firm, 1- to 3-mm papules scattered over the forehead, nose, and cheeks (Figure 1). They began developing at age 30, first on the nose and gradually spreading to the cheeks. At age 36, the patient underwent a biopsy and was informed that the tumors were benign. At age 45 the patient was diagnosed as having “rosacea” and treated with metrogel and minocycline, followed by a 4-month course of isotretinoin, with no improvement. Findings of a second biopsy revealed both trichodiscomas and fibrofolliculomas, consistent with the diagnosis of BHDS. Family history was significant for a father and 2 sisters with similar facial lesions. Medical history included 2 episodes of idiopathic angioedema, but was negative for renal, gastrointestinal, or thyroid problems. Findings of a renal ultrasound examination were within normal limits. His medications included fexofenadine hydrochloride and multivitamins.

A laser skin resurfacing test was first performed on a 3-cm area on the right cheek using the carbon dioxide laser (Coherent Ultrapulse 5000C, Coherent, Palo Alto, Calif) at settings of 300 mJ per pulse, 60 W, with the computer pattern generator handpiece pattern of 2 (parallelogram), size 9 (the largest size), and a density of 5. Post-laser skin resurfacing care included cool water soaks for 20 minutes followed by occlusive ointment (Aquaphor Healing Ointment; Beiersdorf Inc, Wilton, Conn) every 2 to 4 hours. The site reepithelialized within 7 days revealing a relatively smooth surface, and by 6 weeks there was full recovery.

Based on the promising test results, the patient opted for laser skin resurfacing of larger facial areas. The upper cheeks and nose were resurfaced using the carbon dioxide laser at settings of 300 mJ per pulse, 60 W, computer pattern generator handpiece pattern of 2, size 9, and a density of 5 for a total of 2 passes. Individual lesions were then treated with the 3-mm handpiece, settings of 500 mJ per pulse, 3 W, and 3 to 5 passes until lesions were clinically flat. The areas were

Figure 1. Multiple ivory-colored firm papules on the face prior to treatment.
then treated with 1 pass of the Er:YAG laser (CB Erbium/2.94; Continuum Biomedical, Dublin, Calif) at fluences of 5.2 J/cm² (7-mm handpiece, 2 J) overlapping each spot 50%. Postoperative care consisted of cool water soaks and occlusive ointment every 2 to 4 hours while awake until clinically healed (approximately 7 days).

In a second session 2 months later, the patient’s forehead and lower cheeks were treated in a similar manner. Postoperative results were excellent, with substantial flattening of lesions and general smoothing of the skin. There was no hypopigmentation or hyperpigmentation, and no lines of demarcation were noted at 8 weeks of follow-up (Figure 2).

Comment. Birt-Hogg-Dube syndrome is an autosomal dominantly inherited condition characterized by multiple fibrofolliculomas and trichodiscomas, with some patients developing acrochordons and/or hidradenomas. While BHDS is usually a benign condition, individual case reports have documented the presence of renal cell carcinoma and medullary carcinoma of the thyroid. Intestinal polyposis has been reported in 3 cases, and 1 patient affected with multiple fibrofolliculomas and trichodiscomas 8 weeks after laser skin resurfacing.

Comparison of Montelukast and Fexofenadine for Chronic Idiopathic Urticaria

Chronic idiopathic urticaria (CIU) is a troublesome disorder with an unknown etiological agent. Mast cell activation and release of mediators occur in all forms of urticaria. Although histamine is the principal inflammatory mediator of mast cell derivation, other mediators are freed after mast cell activation such as cysteinyl leukotrienes (leukotrienes C₄, D₄, and E₄). We evaluate the efficacy and tolerability of an antileukotriene drug, montelukast sodium, in relation to fexofenadine hydrochloride, an antihistaminic drug, in patients affected by CIU.

Study. Twenty-seven patients affected with CIU were selected; the 4 men and 23 women were aged between 20 and 74 years. The study was conducted for 30 days in double-blind fashion, dividing the patients into 2 groups: 15 took montelukast (10 mg/d), while the 12 patients in the control group took fexofenadine (180 mg/d). All patients underwent a skin test with autologous serum and routine blood chemistry tests before and after the therapy.

The symptomatic profile was evaluated by assigning a score from 0 to 3 to the different symptoms (intensity of pruritus; erythema; and number of wheals [and, if present, their dimensions, elevations, and frequencies of appearance]). In this way, a total symptom score was obtained for each patient by adding the points. The efficacy of the 2 treatments at different times of observation was evaluated using a split-plot model of analysis of nonparametric variance (the Kruskal-Wallis and Friedman tests).

All patients, despite individual variability, presented with progressive improvement of symptoms during treatment. The model of variance analysis (Figure) shows that the reduction of symptoms is highly significant at later times of observation (Friedman test, 72.56; P < .001). The total symptom scores of the patients treated with fexofenadine were on the average worse than those obtained from the
Conclusions. The positive effects induced in CIU by treatment with antileukotrienes, and the reduction in response to the skin test in montelukast-treated patients, could suggest that other mediators besides histamine are involved in the pathogenesis of urticaria. The persistence of positive effects (although to a lesser degree than for antihistamines induced by treatment with antileukotrienes) could indicate that receptor inhibition of newly synthesized mediators can also modulate the cellular releaseability. We conclude that, like asthma, CIU might be effectively treated with antileukotrienes in combination with other drugs, particularly antihistamines.

Is Serum Sickness an Uncommon Adverse Effect of Minocycline Treatment?

Minocycline, a semisynthetic derivative of tetracycline, has become a frequently prescribed medication for the treatment of nodulocystic acne and of persistent acne not responding to tetracycline as its first line of management. It has been associated with serious adverse events, eg, hyperpigmentation of various tissues, autoimmune disorders (systemic lupus erythematosus, autoimmune hepatitis), and serious hypersensitivity reactions (hypersensitivity syndrome reaction, pneumonitis and eosinophilia, and serum sickness). Among these, the number of cases of serum sickness reported in the literature is small in relation to the number of prescriptions of minocycline. However, it is very important that prescribing physicians be aware of the possibility of these uncommon events so that they can recognize the characteristic symptoms at an early stage. Recently, we came across 2 cases of serum sickness after minocycline therapy for severe acne. We herein describe these 2 events.

Report of Cases. Case 1. A 16-year-old girl being treated with minocycline for nodulocystic acne developed fever, urticaria, lymphadenopathy, myalgia, and polyarthralgia on the 14th day. There was no history suggestive of upper respiratory tract infection, fever, any other systemic ailment, nor any other medication regimen in the preceding 3 weeks. The symptoms resolved after a short course of systemic steroid for 5 days.

Case 2. An 18-year-old woman presented with severe urticaria, fever, and polyarthralgia after 10 days of treatment with 50 mg of minocycline twice daily for persisting acne. The symptoms resolved gradually after the treatment was stopped.

Comment. The serum sickness–like syndrome associated with minocycline was first described in 1990 by Puyana et al. These authors excluded other causes that precipitate this syndrome and reported the event in a 19-year-old man with the 4 cardinal features of serum sickness (urticaria, fever, lymphadenopathy, and joint symptoms) after 8 days.

Levenson et al in 1996 reported 2 additional cases of serum sickness due to minocycline. Both patients recovered fully after treatment with an antihistaminic in combination with a brief course of corticosteroid. Hoefnagel et al stressed how important it is for prescribing physicians to be able to recognize the features of serious adverse effects after minocycline treatment.

From the Department of Pediatrics, Children’s Medical Centre of Israel, Petah-Tikva, a study was conducted in...
serum sickness–like reaction associated with minocycline therapy in adolescents. Five adolescents developed a rash and arthralgia/arthritis after taking minocycline for 10 to 30 days. Symptoms resolved gradually after treatment with the medication was stopped. The findings of the migration inhibitory factor assay and mast cell degranulation test were positive in 4 of 5 patients, which is consistent with a role for minocycline in causing these reactions. Shapiro et al.7 theorized that minocycline metabolism may account for the increased frequency of serious adverse events with this drug.

Since the first report of serum sickness–like syndrome associated with minocycline treatment in 1990, not even 9 other cases have been reported. This is probably because the syndrome is being underreported either because of the unawareness of the adverse effects or the lack of willingness of physicians to document the events in their day-to-day practice.

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Results. All patients responded after the introduction of cyclophosphamide (Table 2). One patient (patient 7) needed an increased dose of 20 mg/kg every 3 weeks for 15 weeks to control the disease. Control was obtained in all patients with an average of 6 perfusions (range, 4-10). Associated treatments were decreased in 4 of 9 patients, discontinued in 4 of 9 patients, and kept identical in 1 of 9. Lastly, 7 of 9 patients had complete resolution of the disease after an average of 13 perfusions (range, 5-20), and incomplete resolution was obtained in 2 of 9 patients. No relapse occurred during a medium

Treatement of Cicatricial Pemphigoid With Pulse Intravenous Cyclophosphamide

Cicatricial pemphigoid (CP) is an autoimmune blistering disease that involves the skin and mucous membranes. The prognosis of the disease depends on its location. Oropharyngeal and ocular locations are particularly severe and very difficult to treat. Dapsone is recommended for patients with high-risk lesions. Unfortunately some cases are not controlled by dapsone, or the patient experiences adverse effects. In these cases a combination of systemic corticosteroids and an immunosuppressive agent is required. Oral cyclophosphamide effectively treats pure ocular CP,1,3 and 1 case of successful treatment with pulse intravenous cyclophosphamide has also been reported.4 Here we report a retrospective study of 9 patients presenting with severe and resistant CP successfully treated with pulse intravenous cyclophosphamide.

Patients and Methods. Nine patients with CP were included. Prior treatments that failed to control the disease are listed in Table 1. In 8 of the 9 cases, the disease was not controlled and in 1 case, a relapse occurred as soon as the previous treatment was tapered. Adverse effects occurred in 3 of 9 cases (anemia with dapsone, Quincke edema with sulfasalazine, and depression with corticosteroids). All patients were treated with intravenous pulse cyclophosphamide, 10 mg/kg each month (Table 1). Odanatron (Zophren; Glaxo Wellcome, Marly-le-Roi, France) was used to prevent nausea. In the absence of control of the disease after 4 boluses, intravenous cyclophosphamide was given every 3 weeks, and the dose was increased 25% every 3 boluses. As soon as improvement and control were noted, the associated treatments were tapered (Table 2). The disease was considered controlled if no evolution and no new lesions occurred and to respond if no new lesions and healing of old lesions occurred. Complete resolution corresponded to the disappearance of the clinical signs of CP.

Table 1. Patient Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient No./ Age, y/Sex</th>
<th>Disease Location or Type</th>
<th>Prior Treatment</th>
<th>Duration, wk</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/67/F 25/M/O/G</td>
<td>Prednisone, 1 mg/kg</td>
<td>26</td>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>2/73/F 25/M/O</td>
<td>Prednisone, 1 mg/kg</td>
<td>23</td>
<td>Relapse</td>
<td></td>
</tr>
<tr>
<td>3/70/M 25/M/O</td>
<td>Dapsone, 75 mg Sulfasalazine, 3 g</td>
<td>26</td>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>4/66/F 25/M/O</td>
<td>Dapsone, 175 mg Sulfasalazine, 3 g</td>
<td>27</td>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>5/61/F 25/M/O</td>
<td>Sulfasalazine, 3 g</td>
<td>45</td>
<td>No control, intolerance</td>
<td></td>
</tr>
<tr>
<td>6/81/F 25/M/O/G</td>
<td>Prednisone, 0.5 mg/kg</td>
<td>23</td>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>7/39/M 25/M/O/OP</td>
<td>Prednisone, 1 mg/kg</td>
<td>117</td>
<td>No control</td>
<td></td>
</tr>
<tr>
<td>8/82/M 25/M/O/OP</td>
<td>Dapsone, 100 mg Sulfasalazine, 3 g</td>
<td>12</td>
<td>No control, intolerance</td>
<td></td>
</tr>
<tr>
<td>9/87/F 25/M/G</td>
<td>Dapsone, 250 mg</td>
<td>140</td>
<td>No control</td>
<td></td>
</tr>
</tbody>
</table>

*S indicates skin; M, mouth; O, ocular; OP, oropharynx; and G, genital.

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follow-up period of 59 weeks (8-147). In 3 of 9 patients, cyclophosphamide treatment was discontinued, and no relapse occurred with a follow-up of 24 weeks. Toxic effects are listed in Table 2.

Comment. Cyclophosphamide has been used to treat severe forms of autoimmune blistering diseases.\(^1\)\(^2\) Intravenous pulse cyclophosphamide is associated with fewer adverse effects than is low-dose oral administration. Moreover, orally it takes more time to reach the cumulative dose of 50 g.\(^3\) Cicatricial pemphigoid may be difficult to control with first-line treatment. Patients are subject to blindness or severe tracheal or laryngeal stricture formation.\(^4\) In this retrospective study without a control group, pulse intravenous cyclophosphamide treatment was highly effective in the control of CP recalcitrant to standard therapy with moderate adverse effects.

### Table 2. Patient Response to Therapy With Pulse Intravenous Cyclophosphamide*  

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response/No. of Pulses</th>
<th>Current Status</th>
<th>Follow-up, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C/9, CR/20</td>
<td>C</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>C/5, CR/19</td>
<td>C</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>CR/5</td>
<td>CR</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>C/13</td>
<td>CR</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>C/5, CR/13</td>
<td>CR</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>C/10, C/22</td>
<td>CR</td>
<td>147</td>
</tr>
<tr>
<td>7</td>
<td>C/6</td>
<td>C</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>CR/8</td>
<td>CR</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>C/4, CR/7</td>
<td>CR</td>
<td>8</td>
</tr>
</tbody>
</table>

* C indicates control; CR, complete resolution. Associated treatments were tapered as follows: 10% per month for corticosteroids; 25 mg/mo for dapsone; and 1 g/mo for sulfasalazine. Follow-up corresponds to the period after response to cyclophosphamide treatment (becoming and remaining disease free while under treatment with cyclophosphamide. After CR, the frequency of pulse cyclophosphamide was tapered and then discontinued. No relapse occurred after 24 weeks in 3 patients (patients 3, 5, and 9) after stopping cyclophosphamide treatment.

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**Investigation of Skin Manifestations of Arsenicism Due to Intake of Arsenic-Contaminated Groundwater in Residents of Samta, Jessore, Bangladesh**

Instances of arsenic pollution of groundwater have become worldwide issues. Since the first patient with skin disorders caused by arsenic was found in India in 1983, the Ganges Delta has been recognized as one of the most seriously arsenic-contaminated regions in the world. To investigate the effects of arsenic pollution of groundwater on residents of arsenic-contaminated areas, we examined the residents in Samta Village located in the southwest of Bangladesh, one of the most severely arsenic-polluted districts in the world.

### Subjects and Methods

From February 14 to February 16, 1998, we examined the residents in Samta Village (population, 3555 [1837 men, 1718 women]). The total number of participants was 135 (82 male, aged 10 to 70 years—mean age, 34.8 years; 53 female, aged 6 to 60 years—mean age, 33.1 years). They were selected in advance on the suspicion of arsenicism in the preliminary examinations by the members of regional health institute. For malignant skin lesions, diagnosis was made clinically.

### Results

A summary of the clinical manifestations of arsenicism on the skin and in the oral cavity is given in the Table. Of 135 participants, all except 1, a 26-year-old

### Clinical Manifestations of Arsenicism Among 135 Participants*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>82</td>
<td>53</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>34.8</td>
<td>33.1</td>
</tr>
<tr>
<td>Youngest</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Oldest</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Cases with skin color abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>80 (97.6)</td>
<td>52 (98.1)</td>
</tr>
<tr>
<td>Leukomelanosis</td>
<td>59 (72.0)</td>
<td>35 (68.6)</td>
</tr>
<tr>
<td>Cases with pigmentation in oral cavity</td>
<td>26 (31.7)</td>
<td>14 (26.4)</td>
</tr>
<tr>
<td>Cases with hyperkeratosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic</td>
<td>10 (12.3)</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Extremities (not including hand and foot)</td>
<td>9 (11.0)</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>Hands</td>
<td>73 (89.0)</td>
<td>48 (90.6)</td>
</tr>
<tr>
<td>Feet</td>
<td>77 (93.9)</td>
<td>51 (96.2)</td>
</tr>
<tr>
<td>Cases with malignant skin lesion(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>6 (7.4)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Multiple</td>
<td>9 (11.0)</td>
<td>4 (7.5)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number (percent).
man, demonstrated some skin abnormalities typical of arsenicism. Concerning malignant skin lesions, 23 residents were clinically diagnosed as having malignant disorders: 15 men (aged 24 to 65 years) and 8 women (aged 35 to 55 years). Furthermore, 13 patients (9 men and 4 women) had multiple lesions.

Comment. Arsenic is a natural element, and inorganic arsenic is much more toxic than the organic type. Inorganic arsenic exists in 2 forms: arsenite \([\text{As(III)}]\) and arsenate \([\text{As(V)}]\).1 Both \text{As(III)} \text{and As(V)} are readily taken up by cells, in which \text{As(V)} is rapidly reduced to \text{As(III)}.1 Arsenite is much more toxic than \text{As(V)},1 and it is thought to exert its cytotoxic and genotoxic effects by binding to sulfhydryls, resulting in protein denaturation and inhibition of enzyme activity.1-4

Most of the arsenicism in the Ganges Delta has been caused by drinking well water contaminated with inorganic arsenic; the predominant form of arsenic detected in well water is 90% \text{As(V)}.5 Of the 23 cases of malignant skin lesions, 21 were in the early stages of disease comparable with carcinoma in situ. One 38-year-old woman had more than 10 basal cell epitheliomas (Figure), and a 55-year-old woman had squamous cell carcinoma on her parietal area.

Among 282 tube wells in Samta Village analyzed for arsenic concentration level, only 23 contained water found to have below a 0.05-mg/L arsenic concentration level: the standard safety value established by the World Health Organization. Furthermore, in as many as 49 wells, arsenic was detected above a concentration level of 0.5 mg/L.

In conclusion, we stress that arsenic pollution in the Ganges Delta is extremely serious. It is urgent that we find ways to provide safe drinking water for the residents of this area.

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1. Hu Y, Su L, Snow ET. Arsenic toxicity is enzyme specific and its effects on ligation are not caused by the direct inhibition of DNA repair enzymes. Mutat Res. 1998;408:203-218.

A 38-year-old woman with multiple basal cell epitheliomas. More than 10 lesions were identified.