

ultraviolet exposure (ie, “exogenous” pathway). Previous studies have indeed shown a steady increase followed by a decrease in the number of nevi before and after midlife, respectively. Today, many researchers are of the opinion that intermittent rather than long-term sun exposure is the key factor in the development and disappearance of nevi. It is theorized that intermittent ultraviolet exposure may cause *BRAF* mutations in melanocytic stem cells at the dermoepidermal junction. This in turn may cause the mutated stem cell to proliferate and form a nevus; however, if the host’s cell-cycle checkpoint regulators are functioning normally, the cells would eventually enter senescence.⁴ Furthermore, it has been observed by many researchers that these true “acquired” nevi often undergo spontaneous regression later in life. These observations explain not only the high prevalence of junctional nevi on skin sites that are not chronically sun exposed found in the study by Westhafer et al,¹ but also explain the peak incidence of junctional nevi they observed during midlife.

In sum, the results reported by Westhafer et al can be plausibly explained in the view of our dual concept of nevogenesis.² Finally, we agree with the authors that our current concept of nevus classification requires revision and we have proposed therefore a new classification of nevi based on dermoscopy.⁵

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Transdermal delivery of *Clostridium botulinum* toxin type A by pulsed current iontophoresis

To the Editor: In a pilot study recently published in the *Journal*, Kavanagh and Shams¹ reported that botulinum neurotoxin (BoNT) could be delivered in humans by iontophoresis to treat palmar hyperhidrosis with obvious advantages over the use of injection. Although the authors observed significant clinical effects, no data are yet available demonstrating the actual transdermal passage of BoNT. Herein we demonstrate that iontophoresis allowed the delivery of BoNT type A (BoNT/A) through living rat skin. We used a Food and Drug Administration (FDA)—approved pulsed current iontophoresis drug delivery system (FDA approval No. K042590, October 14, 2004, Transderm Ionto System, Mattioli Engineering, McLean, Va).

Experiments were performed according to Principles of Laboratory Animal Care in compliance with the Commission for Animal Experiments of the University of Firenze. Experiments were performed on male Wistar rats (Harlan, Udine, Italy), age 6 to 8 months, weight 350 ± 50 g.

Pulsed current iontophoresis was performed for 10 minutes following a standard procedure.² Forty units per milliliter of BoNT/A (Vistabex, Allergan Inc, Irvine, Calif) was applied on all selected skin areas. In each experiment, one of the areas was treated with iontophoresis; on the other area, selected as the control area, no electric treatment was performed. Full-thickness biopsy specimens were obtained from treated and control areas soon after application of iontophoresis. Biopsy specimens were soaked and washed several times with phosphate-buffered saline solution, fixed, embedded, and frozen. Sections were stained with hematoxylin-eosin solution. Immunohistochemical reaction was performed by using a monoclonal antibody against BoNT/A (US Biological, Swampscott, Mass), and a biotin/avidin

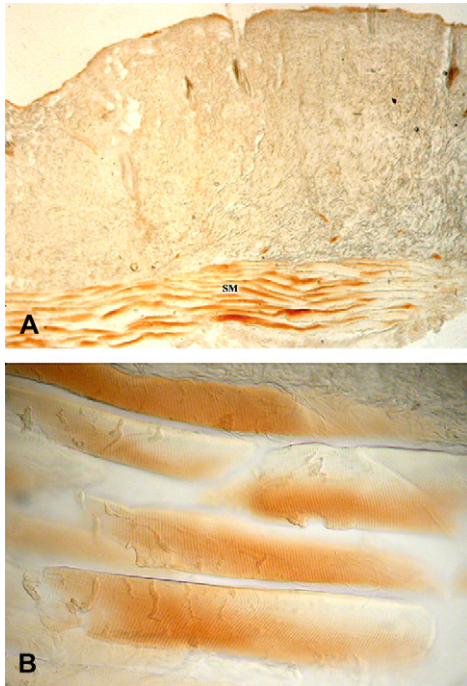


Fig 1. Association of BoNT/A with cutaneous skeletal muscle fibers. **A**, After iontophoresis, BoNT/A was detected in association with skeletal muscle fibers (*SM*) localized in deep dermis; fibers appeared brown with staining. **B**, Details of skeletal muscle fibers; typical aspect of actin/myosin complex is evident. (**A** and **B**, Immunohistochemical reaction; original magnifications: **A**, $\times 40$; **B**, $\times 400$.)

system detection kit (Vectastain ABC, Vector Laboratories, Burlingame, Calif). Specimens were observed by a light microscope.

After iontophoresis, the neurotoxin was clearly detected in association with cutaneous striated skeletal muscle fibers localized in the deep dermis of rat's skin (Fig 1, *A*). Muscle fibers appeared intensely stained, and the characteristic aspect of the actin/myosin complex was evident (Fig 1, *B*). A weak immunohistochemical reaction indicating the presence of BoNT/A was evident at the site of application (ie, at the level of the epidermis) (Fig 2, *A*) and in association with the hair roots, with sebaceous glands, and with the arrector pili muscle fibers (Fig 2, *B*). BoNT/A could not be detected in biopsy specimens taken from negative controls. The presence of a positive immunohistochemical reaction at the level of the epidermis in the iontophoresis-treated samples could be interpreted as if iontophoresis "forced" the neurotoxin through the epidermis, possibly inducing the formation of new pores³ through which even large molecules could be carried.⁴ The presence of a strong immunohistochemical reaction at the level of adnexa is consistent with the notion that hair and adnexa represent a

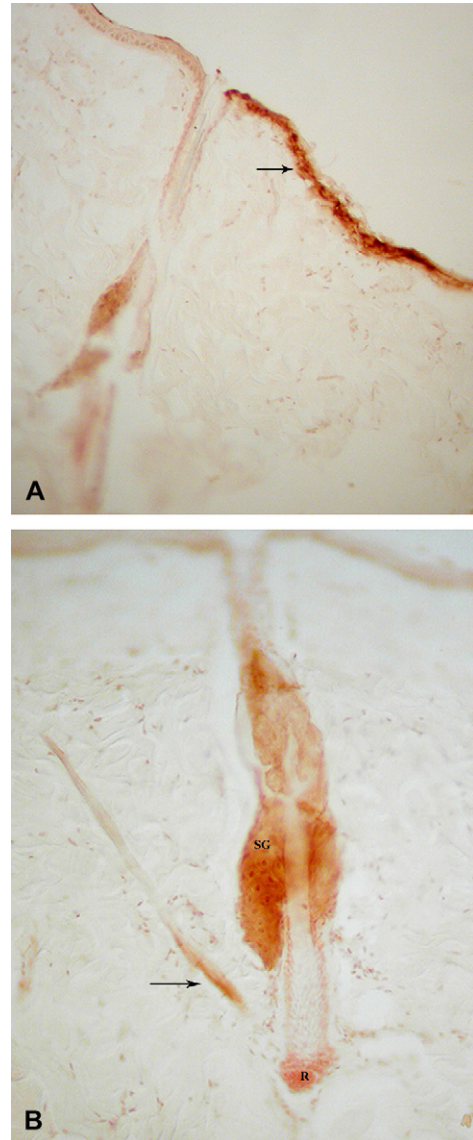


Fig 2. Association of BoNT/A with epidermis and adnexa. **A**, BoNT/A, after iontophoresis, was evident at the site of application (ie, epidermis) (*arrow*). **B**, BoNT/A was also associated with appendages such as the hair root (*R*) and sebaceous gland (*SG*); *arrow* indicates arrector pili muscle. Immunohistochemical reaction. (Magnifications: **A**, $\times 100$; **B**, $\times 200$ [+ zoom].)

preferential pathway for molecules undergoing iontophoresis through mammal skin.⁵ As far as the animal model is concerned, although certain interspecies differences in skin permeability are well documented, for practical and legal purposes it is assumed that human skin absorption is equal to rat in vivo dermal absorption.⁶ We are unable to establish whether the electrical treatment modified the chemical structure or the biological properties of BoNT/A. However, in their report, Kavanagh and Shams¹ demonstrated a significant effect of

iontophoresed BoNT/A, thus lending credit to the hypothesis that iontophoresis did not abolish its biological activity.

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CASE LETTERS

Secondary syphilis presenting as scrotal eczema

To the Editor: Syphilis remains a worldwide problem despite the advent of effective treatments, many diagnostic tests, and the development of educational public health programs.¹ The diverse clinical manifestations of syphilis are one of the causes of this prevalence. We report 2 cases of secondary syphilis that showed unusual presentations that, to the best of our knowledge, have not been reported before.

A 37-year-old male was referred to our outpatient clinic with a several-month history of a pruritic erythematous plaque with several small papules on his scrotum (Fig 1, A). He had been clinically diagnosed with scrotal eczema and treated with topical steroids and oral antihistamines without any improvement. We performed a biopsy and the pathologic diagnosis was chronic dermatitis. We prescribed a more potent topical steroid and oral antihistamine, but we could not determine the efficacy of this treatment because he was lost to follow-up. Several months later, the patient returned to our clinic; although his scrotal lesions were mildly improved, he was noted to have condylomata lata perianally. His previous biopsy was reviewed and irregular epidermal hyperplasia with focal spongiosis, a lichenoid and periadnexal inflammatory infiltrate composed of lymphocytes, histiocytes, and plasma cells, and hyperplasia of the endothelial cells were noted (Fig 2, A and B). A

serology test revealed a reactive Venereal Disease Research Laboratory (VDRL) test with a titer of 1:8 and a positive *Treponema pallidum* hemagglutinin assay (TPHA).

The second patient was a 41-year-old male who presented with a scrotal lesion that resembled the first patient's lesion (Fig 1, B). On physical examination, a few erythematous annular patches were found on his palms and soles, which were characteristic of secondary syphilis. The VDRL titer was 1:128 and the TPHA was reactive. The histopathologic findings of the scrotum revealed lichenoid and granulomatous cellular infiltrations composed of plasma cells, lymphocytes, and histiocytes. Both patients had not experienced any genital ulcer history and they were in good health save for the skin manifestations.

Our differential diagnosis for these eczematous scrotal lesions included lichen simplex chronicus, Hailey-Hailey disease, tinea cruris, and extramammary Paget's disease. Fungal organisms, acantholysis, and Paget's cells were not detected on biopsy. The extensive number of plasma cells in the dermal infiltrate and the positive VDRL in both patients supported the diagnosis of secondary syphilis. All their skin lesions resolved after treatment with benzacillin penicillin.

Secondary syphilis is often called "the greater imitator" because it shows a variety of clinical