Iontophoresis in dermatology

A review

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Iontophoresis, the process of increasing the penetration of drugs into surface tissues by the application of an electric current, has been applied to a great many disease conditions over its 200-year history. Although its greatest success has been in the treatment of hyperhidrosis, it is steadily finding new applications. Many aspects of the mechanisms of iontophoresis have yet to be studied before the technic is both fully understood and maximally utilized. In this article we review the literature on iontophoresis as it pertains to dermatology, including the basic principles, engineering aspects, physicochemical principles, and clinical applications. (J AM ACAD DERMATOL 15:671-684, 1986.)

HISTORIC REMARKS

Iontophoresis (Gr. introduction of ions) is defined[1] as the introduction, by means of an electric current, of ions of soluble salts into the tissues of the body for therapeutic purposes. This process is also called iontherapy, galvanoionization, ionic medication, and medical ionization. In the medical literature the term *iontophoresis* is used to indicate the process of increasing the penetration of electrically charged drugs into surface tissues by the application of an electric current. The technic was apparently first described in 1747 by Veratti.[2] This idea fit well into the scientific spirit of 18th century Italy, when Galvani did his famous experiment with dissimilar metals connected by an electrolyte, and Volta constructed the first electric cell. As a result of these inventions, by the 19th century galvanism had become very popular and was used for the treatment of neurologic, gynecologic, and genitourinary disorders, as well as for electrochemical destruction.

This technic temporarily lost its popularity toward the end of the 19th century when more sophisticated inventions in the field of electricity were made. Iontophoresis was revived at the beginning of the 20th century by Leduc,[3,4] who introduced the term *iontherapy* and formulated laws that govern this process. He proved that ionic "medications" penetrate the skin and may exert local and systemic effects. In his classic experiment he used two rabbits connected in series with an iontophoresis machine. The first rabbit had strychnine sulfate on the electrode between it and the machine. The second rabbit had potassium cyanide on the analogous electrode. When a current of 40 to 50 mA was turned on so that the first rabbit had the positive electrode over the strychnine and the second rabbit had the negative electrode over the cyanide, the first rabbit was seized by tetanic convulsions because of introduction of strychnine ion, while the second rabbit died rapidly with signs of cyanide poisoning. The two animals were then replaced by new ones and the current flow as reversed. Under these conditions the animals were unharmed. This elegant experiment provided convincing evidence that iontophoresis was a powerful technic for the introduction of drugs into and through the surface tissues. This discovery stimulated a new wave of enthusiasm

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for iontophoresis and subsequently led to numerous applications, some of which are described in this review.

The interest in iontophoresis has waxed and waned during the 20th century. Presently, we are witnessing yet one more rediscovery phase—hopefully a long-lasting one, because this simple technic has much to offer and still awaits elucidation of its intricacies. Among dermatologists iontophoresis has best found acceptance for its application in the treatment of hyperhidrosis, although the mechanism of its action has remained enigmatic.[5,6]

In this article we review the literature on iontophoresis as it pertains to dermatology, including the basic principles, engineering aspects, physicochemical principles, and clinical applications.

BASIC PRINCIPLES OF IONTOPHORETIC TREATMENT

Iontophoresis involves delivery of selected ions into tissues by passing a direct electrical current through a medicated solution and the patient. This method of drug administration has many advantages. Systemic side effects of drugs are significantly decreased because only minute amounts of drugs are delivered, while a relatively high drug concentration is administered locally where it should achieve the maximum benefit. Patient acceptance is generally excellent, and fear of injection is eliminated.

The technic follows. Drug is applied under an electrode of the same charge as the drug, and a return electrode opposite in charge to the drug is placed at a neutral site on the body surface. The operator then selects a current below the level of the patient's pain threshold and allows it to flow for an appropriate length of time. The electrical current significantly increases the penetration of the drug into surface tissues.

The two classically considered prerequisites for iontophoretic treatment are that the drug must be charged (or modified to carry a charge) and the disease process must be at or near a body surface. However, the results of investigations reported by Gangarosa et al[7] and Glass et al[8] showed that these conditions may be modified.

Gangarosa et al[7] showed that nonelectrolytes [^{3}H]9-β-D-arabinofuranosyladenine (Ara-A) and [^{3}H]thymidine(dThd) can be iontophoretically delivered to mouse tissues in aqueous NaCl solutions. This process is termed *iontohydrokinesis* and involves passive movement of nonelectrolytes in association with water or with moving ions. It can be conceptualized with the use of the following model: Both negative and positive ions carry water molecules, the number being proportional to the size of the ion's hydration shell. Ions, along with the water molecules arrayed around them, then move in the electric field and passively carry nonelectrolytes by a mass transport effect. Thus the condition requiring the drug to be charged can be modified to include nonelectrolyte drugs in solutions of charged molecules.

The disease may not have to be close to a body surface in view of the results presented by Glass et al.[8] These investigators showed that dexamethasone sodium phosphate iontophoretically delivered to monkey's joints, although found predominantly in the skin, also penetrated to the joint capsule and cartilage and hence might prove useful in the treatment of inflammatory joint diseases. Thus, the condition requiring the disease process to be at a body surface can be modified to include diseases involving tissues close to and attached to the skin (e.g., bursae, ligaments, joint capsules, etc.) as suitable for iontophoretic treatment.

The ultimate suitability of a given drug for iontophoretic application must be tested in vivo. However, selection of drugs appropriate for such testing can be based on their specific conductivities, which give an estimate of how easily the drugs move in solution when an electric current is applied.[9] The dimensions of this quantity are the amount of electricity transferred per unit time across unit area per unit potential gradient applied to the given solution. Therefore, the specific conductivity of a drug should be directly proportional to its suitability for iontophoretic administration. Gangarosa et al[9] provide a useful reference for selection of drugs for potential testing by listing specific conductivity values for a number of local anesthetics, vasoconstrictors, corticosteroid hormones, antineoplastic drugs, nucleotides, and antiviral agents.

IONTOPHORESIS UNITS

The classical paper by Levit[5] describing the design of an iontophoresis device dates back to 1968. He designed a simple iontophoresis machine for the treatment of hyperhidrosis that consisted of a direct current power source able to pass several milliamperes of current through the patient's skin. Significant advances in the design of iontophoresis units have been made since then, proceeding along the lines of technologic advancements as well as detailed requirements for Food and Drug Administration (FDA) clearance and product insurance. Currently three types of iontophoresis units are commercially available: line-operated units, simple battery-operated units, and rechargeable power sources.

Line-operated units are widely used for pilocarpine iontophoresis sweat testing in cystic fibrosis.[10] Pilocarpine devices for iontophoresis have safety-protected circuits with well-grounded three-pronged plugs. Although objective evidence indicates that such devices are safe, there has been concern that some patients may think that there is a danger of electric shock from being connected to the wall outlet. For this reason battery-operated units have become popular in the 1980s.

A reasonably priced commercial unit, called the Drionic device, was recently introduced for home treatment of hyperhidrosis by the General Medical Company (Los Angeles, CA). This device was tested by Walter Reed Army Medical Center and the results were published by Peterson et al.[11] The Drionic device consists of a battery-operated generator acting as the current source. The current is delivered to the hyperhidrotic area through a tap water medium that is contained in wool pads suspended in small plastic boxes.

A more sophisticated multipurpose iontophoresis device for medicine, dentistry, and physical therapy was introduced by Motion Control Inc. (Salt Lake City, UT). Called Phoresor, it is powered by a 9-V replaceable battery with circuitry converting this voltage through a setup transformer to 45 V DC. The Phoresor delivers a constant current and automatically adjusts to any change in resistance in the external circuit during the procedure. It has a digital current readout, low-battery warning light, and an audible signal if the battery is placed backwards. All these features make it a very versatile, practical, and convenient unit for office use. For a more detailed description of Phoresor, the reader is referred to "Iontophoresis in Dental Practice" by L. P. Gangarosa Sr.,[12] which also provides a comprehensive comparison of currently available iontophoresis power supply and systems, including rechargeable power sources.

Those desiring information regarding automatic control of the treatment are referred to the paper by Craig and Collie,* which provides detailed circuit diagrams for an iontophoresis unit capable of timing the treatment period and automatically reversing the current. This iontophoresis unit also incorporates a number of patient safety features, such as limiting the maximal rate of change of current to 2 mA/sec to prevent shock and requiring the current setting to be returned to zero before treatment can be started. Because this is a wall unit device, some patients may have the reservations we have mentioned about using it.

PHYSICOCHEMICAL ASPECTS OF IONTOPHORESIS

Iontophoresis has been used in various fields of medicine.[9,13] Some of the earlier experiments aimed at creating new applications for iontophoresis were carried out at the turn of the century by Leduc.[3,4] Systematic attempts at understanding the quantitative physicochemical aspects of this technic, however, were not initiated until half a century later, and their extent has been rather limited.

In 1954 O'Malley et al,[14] with the use of iontophoresis, introduced ^{32}P, ^{24}Na, ^{131}I, and ^{45}Ca into rat skin and demonstrated the presence of these isotopes in various tissues of the experimental animals. The distribution pattern resembled that of isotopes administered by other routes. In 1955 O'Malley and Oester,[15] using iontophoresis of ^{32}P in rats and measuring its concentration in the urine, demonstrated that the radioactive substance distribution in the tissues was proportional to the current density, the duration of iontophoresis, and the concentration of the radioactive phosphorus. This

*Craig DL, Collie JW: An iontophoresis unit for the treatment of hyperhidrosis. Australas Phys Eng Sci Med 6(3):125-127, 1983.

type of study was extended to human subjects several years later when Zankel et al[16] studied the absorption of ^{131}I delivered via iontophoresis by measuring the concentration of radioiodine in the urine (after saturation of the patient's thyroid with stable iodide). They concluded that under optimal conditions iontophoresis resulted in systemic absorption of 5% of applied iodine while 4% remains on the skin immediately after the treatment.

In an attempt to study the mechanism of iontophoresis and the factors that govern this process, the same group conducted another study in 1963[17] and concluded that the absorption of ^{131}I could be reduced by prior application of heat, ultrasound, or histamine iontophoresis. Similarly, cold application could increase its absorption. Because the former agents enhance sweat secretion and cold decreases the rate of sweat production, these findings point to the sweat glands as the most significant paths for conduction of charged ions into and through the skin. This conclusion was confirmed by Papa and Kligman,[18] who showed that methylene blue introduced into the skin via iontophoresis entered sweat glands in a punctate pattern and outlined the sweat pores.

In more recent work on the mechanism of action of iontophoresis, Puttemans et al[19] studied the fate of potassium iodide impregnanted on sponges and applied to human joints. They demonstrated that iontophoresis did not result in superficial migration of the applied ions from one pole to the other but led to penetration into the skin. Iodine ion-selective electrodes were used to measure concentrations of iodine in experimental solutions, and x-ray fluorescence scans were performed to establish uptake of I^- by the thyroid. Minimal differences in uptake were observed for each patient with subsequent applications, whereas the interindividual differences were more pronounced. Collective evidence from all experiments suggested that, of the applied potassium iodide, 10% had penetrated the skin.

Wahlberg[20] compared the iontophoretic and epicutaneous administration of chromate and sodium isotopes. He sought experimental support for the hypothesis that iontophoresis was an efficacious means of administering test substances in the investigation of obscure cases of contact dermatitis. This study focused on two aspects of this process. First, a quantitative comparison was made between iontophoretic and topical administration of chromium and sodium isotopes. The amount of chromate absorbed was forty-three times greater with iontophoresis than with topical administration. Similarly, the amount of sodium absorbed was increased by a factor of seven. He then studied the rate of absorption as a function of current strength and treatment duration. In the case of chromium, both increased current strength and treatment duration correlated with increased rate of absorption of isotope ions. In contrast, the rate of sodium absorption attained maximal values at relatively low current strengths and treatment durations. These differences were attributed to the fact that, while the sodium ion is nonirritating and therefore freely diffusible, chromate is known to irritate tissues and can denature and precipitate proteins. The presence of chromate appears to open the channels through which the ion undergoes electrophoresis and thus facilitates the movement of additional chromate. Wahlberg concluded that iontophoresis can be used as a test method for the investigation of contact dermatitis.

In summary, iontophoresis has been shown to be a reliable method for delivery of substantial amounts of drugs into tissues. Sweat glands seem to be the most significant, but not exclusive, path for conduction of charges into and through the skin. Freely diffusible ions do not alter the structure of their conduction paths as evidenced by the reproducibility of their delivery rates. In contrast, protein precipitators significantly alter the electrical properties of the skin. The intricacies of the mechansim of iontophoresis await further studies.

DERMATOLOGIC APPLICATIONS OF IONTOPHORESIS

History. Iontophoresis has been used for the treatment of various dermatologic conditions (Table I). Unfortunately, the majority of published studies are either uncontrolled series or anecdotal observations. During the first half of this century, simple ions and heavy metals were the most frequently used drugs. Over the last 30 years, however, the interest in iontophoresis has shifted toward its use as a drug delivery system for a wide

Table I. Summary of conditions treated via iontophoresis

Condition	Chemical	Results and comments	Reference
Ischemic ulcer	Zinc oxide	Case report; wound closure	27
Ulcers	Histamine	Complete healing in 4/5 patients; uncontrolled small series	28
Plantar warts	Sodium salicylate	Case report; resolution of lesion	32
Aphthous stomatitis	Methylprednisone	Complete healing in several days; uncontrolled small series	12
	Triamcinolone	Immediate relief in prodromal stage; controlled vs no treatment	46
Lichen planus	Methylprednisone	Erosive oral lichen planus healed with fibrosis; uncontrolled small series	12
Peyronie's disease	Hydrocortone phosphate	11/12 patients marked improvement; uncontrolled study	48
Local skin anesthesia	Lidocaine with epinephrine	Markedly superior to either drug alone with or without current or both drugs without current; controlled study	68
Vitiligo	Meladine	Marked return of pigmentation in compliant patients; uncontrolled	75
Scleroderma	Hyaluronidase	Increased skin softness and decreased cold sensitivity on treated side	76
Lymphedema	Hyaluronidase	Progressive reduction in volume of the treated extremity; controlled study	77
Pigment for dermabraded tattoos	Iron and titanium oxides	Mostly unpredictable; uncontrolled study	79
Scar tissue	Iodine	Case report; bunionectomy scar; improvement in the range of motion and increase in muscle strength of treated joint	80
Infected burn wound	Penicillin	Double-blind study on humans and rats; 200-fold increase in penicillin concentration in iontophoresis group	81
Sweat test	Pilocarpine	Rapid sweating for 30 minutes; controlled	84

variety of medications, ranging from steroids to antibiotics to local anesthetics.

Zinc iontophoresis was used earlier for the treatment of lupus vulgaris[21] and skin neoplasms.* Thallium iontophoresis was applied for epilation[22] until total hair loss secondary to toxicity was observed. In the preantibiotic era, a variety of infectious conditions were treated by the iontophoresis of metals. An example is streptococcal infections, which were treated with copper sulfate iontophoresis after surgical debridement.[21] Electrodeposition of copper on the surface of genitalia was investigated for the treatment of venereal diseases,[23] and a quieting effect on perineal and anorectal pruritus was observed with bromide, salicylate, and aconitine iontophoresis.[21]

Iodine and zinc and copper iontophoresis were once used to accelerate healing and to disinfect poorly healing wounds and ulcers. For this treatment British physicians used very strong currents, 100 to 200 mA, and general anesthesia.[21]

Ulcers. Ionic transfer has more recently been used for the treatment of patients with ischemic leg ulcers.[24-28] Cornwall[27] reported a case of a 71-year-old man with bilateral below-knee amputations secondary to diabetes mellitus and peripheral vascular disease who presented with ischemic ul-

*Friel AR: The treatment of septic surfaces by zinc ionization. Br J Actinotherapy 5:167-168, 1930.

Table II. Animal studies of iontophoresis

Condition	Drugs used	Current and duration	Treatment	Results	Subjects	Reference
Patch testing for contact eczema	51_{Cr}	2 mA for 5 min	Repeated experiments	43× greater absorption iontophoretic over epicutaneous administration	Guinea pigs	20
	22_{Na}	2 mA for 5 min	Repeated experiments	8× greater absorption iontophoretic over epicutaneous administration		
Demodex folliculorum	2% methylene blue	30 mA for 5 min	Single treatment	Regression of lesions; reduction in mite population	3 dogs; 24 skin areas	31
Trichophyton verrucosum	Potassium iodide	30 mA for 5 min	Single treatment	Marked reduction in intracellular spores	13 calves	
HSV-1 and HSV-2	Ara-AMP iontophoresis vs controls: Ara-A gel and ointment, topical idoxuridine, placebo, and no treatment	Not given	Iontophoresis: once daily for 3 days; controls: twice daily for 5 days	Significant increase in survival time and decrease in number of lesions and their size	10 mice/group	33 35

HSV: Herpes simplex virus.

cers over both tibial crests, one measuring 15.6 cm^2 and the other 7.74 cm^2. Using a 4- to 5-mA current and a 15-minute treatment time, a 0.1 M solution of zinc oxide was introduced by iontophoresis twice daily, 6 days a week for 20 days. This resulted in a greater than 98% closure of the ulcers.

The effect of histamine iontophoresis on ulcers was studied by Abramson et al.[28] A series of fourteen patients with ulcers from varying causes were treated with histamine diphosphate (1:10,000 dilution) iontophoresis with the use of currents between 3 and 12 mA for 5 to 12 minutes and treatments given two or three times a week for several months. Each treatment was preceded by 15 minutes of whirlpool therapy and debridement of necrotic tissue. Complete healing was reported in four of the five patients with progressive systemic sclerosis, and some improvement was observed in the remaining subject. All four patients with sickle cell anemia responded satisfactorily to the therapy, as did a patient with diabetes mellitus and arteriosclerosis obliterans, as well as a patient with venous stasis ulcers. Three patients with vascular ischemic lesions showed no improvement.

Infections. Fungal infections also have attracted the attention of iontophoresis enthusiasts; there are reports of successful treatment of epidermophytosis with the use of copper sulfate iontophoresis[29] and sporotrichosis with potassium iodide iontophoresis.[30] These results have encouraged veterinarians to reexplore iontophoresis for the treatment of fungal infections, with reports of the alleviation of *Trichophyton verrucosum* infection from bovine skin by potassium iodide iontophoresis and the eradication of heavy infestation of *Demodex folliculorum* from canine skin by methylene blue iontophoresis[31] (Table II).

The treatment of warts has been a challenge for a long time. In the first half of the 20th century, magnesium iontophoresis was tried with good results.[21] More recently, successful treatment of plantar warts with sodium salicylate iontophoresis was reported.[32] With the use of a current of 1 mA,

Table III. Iontophoretic treatment of herpes simplex

Reference	Chemical	No.*	Current and time	Regimen	Results	Comments
39	Idoxuridine 0.1%	25	0.6 mA for 15 min	Single treatment	26/28 major positive	Uncontrolled study; 32 lesions total
	Acyclovir (5% Zovirax)		0.6 mA for 15 min	Single treatment	4/4 major positive	
12, 37	Idoxuridine 0.1%	6	1.0 mA for 10 min	1-2 treatments	63% reduction in healing time	Uncontrolled study
36	Idoxuridine 0.1%	5	0.5-0.8 mA for 10 min	Single treatment	Relief of discomfort; reduction in healing time	Controlled study; iontophoresis vs no treatment
	Levamisole	3	0.5-0.8 mA for 10 min	Single treatment	"Promising results"	Uncontrolled study
38	Idoxuridine 0.1%	54	0.5 mA for 7 min	Single treatment	70% reduction in healing time	Uncontrolled study

*Number of patients in the study.

a 2% aqueous solution of sodium salicylate was administered for 10 minutes once weekly to five patients with plantar warts. The authors noted that four patients required two treatments each and the fifth patient needed three treatments before the warts came off.

A series of papers on the iontophoretic application of antiviral chemotherapeutic agents for the treatment of herpes simplex virus infection in mice was contributed by Hill et al,[33] Park et al,[34] and Gangarosa et al[35,36] (Table II). Gangarosa's group extended these studies to patients and reported that iontophoretic application of idoxuridine was effective in aborting episodes of herpes simplex lesions.[12,37] More recent studies on iontophoresis of iodoxuridine for the treatment of herpes labialis[38,39] appear to support these findings (Table III). Gangarosa's group also carried out extensive work on animal models to elucidate the mechanism of herpes simplex virus latency, reactivation, and recurrences with the use of epinephrine iontophoresis to rabbit eyes.[40-45]

Lekas[46] reported relief of discomfort and reduction in healing time of herpes simplex lesions in a small group of patients enrolled in a controlled study and treated by iontophoresis of idoxuridine, 0.5 to 0.8 mA for mucocutaneous areas and 0.2 mA for oral lesions for 10 minutes. Lekas[46] also conducted, on five patients, an uncontrolled study of levamisole iontophoresis for the treatment of both herpes simplex and recurrent aphthae and reported promising results.

Glucocorticosteroids. Lekas[46] studied a small group of patients with aphthous stomatitis who were treated with iontophoresis of triamcinolone acetonide, 0.2 mA for 10 minutes, with immediate relief of discomfort in the prodromal stage. For lesions beyond the prodromal stage, symptomatic relief was not achieved until after 36 hours. Another study of corticosteroid iontophoresis for the treatment of aphthous stomatitis and lichen planus conducted by Gangarosa[12] is summarized in Table I.

Glass et al[8] suggested that iontophoresis may be an efficacious and desirable method for administration of steroids to localized regions of inflammation. These investigators anesthetized a Rhesus monkey and placed positive test electrodes containing tritium-labeled dexamethasone and lidocaine over the clipped skin of five joints on the right side of the body. Control electrodes containing the same compounds were placed on the left side. Five milliamperes of current were applied to the test electrodes for 20 minutes and then the animal was sacrificed. A postmortem iontophoresis of one joint was performed under the same conditions as described. All the joints studied were dissected down to and including the bony struc-

Table IV. Iontophoretic treatment of hyperhidrosis

Reference	Chemical	No.*	Current and time	Regimen	Results	Comments
53	Poldine methyl sulfate 0.5% in H_2O	NG	5-20 mA for 15 min	Weekly 6-8 wk	75% decrease in sweating for 3 mo or longer	Uncontrolled study; mouth dryness
6	Poldine methyl sulfate 0.05%-0.075% tap water	22	15-20 mA for 15 min	1-2×/wk for 6-8 wk	8/22 improved with conventional treatment; poldine more effective than tap water for unresponders; treatment with poldine most effective on palms and least on axillae	Controlled study; opposite side either untreated or treated vs conventionally; mouth dryness with poldine
54	Atropine sulfate 0.1, 0.5, and 1.0 mg in 10 ml H_2O	6	5 mA for 15 min	5-10 exposures in hot chamber for 1 hr each	0.1 mg no significant difference; 0.5 mg significant difference after 20-30 min; 1.0 mg significant difference during entire experiment	Controlled study; opposite side untreated and served as control
†	Glycopyrronium bromide 0.05% in H_2O	NG	Adult, 12 mA for 12 min; child, 6 mA for 12 min	4 wk to several mo	Excellent	Uncontrolled study; series extending over 10 yr; mouth and throat dryness
	Tap water	NG	Same as above	1-2/wk	Satisfactory	Same series as above; no side effects
51	Tap water	26	Adult, 15-20 mA for 15 min; child, 7-12 mA for 15 min	Twice weekly up to 6 mo	To achieve hypohydrosis: palms, 7 treatments; soles, 9 treatments; axillae, 12 treatments	Uncontrolled study; repeated treatments required every few days to achieve satisfactory results

NG: Not given.
*Number of patients in the study.
†Morgan, K: The technic of treating hyperhidrosis by iontophoresis. Physiother 66(2):45, 1980.

tures. The specimens were then dissected into tissue layers and the amount of drug per unit weight of tissue was measured. The concentrations below test, as compared to control, electrodes were significantly higher ($p < 0.05$ in most cases). Blood flow seemed to have little effect on the result of the experiment as the ante- and postmortem amounts of drug introduced by iontophoresis were comparable. Less than 0.4% of the drug was detected in the total blood volume at the end of the experiment, also leading one to conclude that iontophoretic transfer, rather than redistribution via the vascular system, was the mechanism for penetration into the joint capsule.

The safety of steroid iontophoresis in diseases of the subcutaneous tissues was demonstrated by Murray et al.[47] The study involved twenty patients who, when first seen, had symptoms compatible with noninfectious connective tissue pathology such as synovitis and tendonitis. The location of the involved tissue was estimated to be 1.25 cm or less beneath the surface of the skin. Commercial preparations of dexamethasone, hydrocortisone, and prednisolone were used with current intensities, and treatment durations varied between 3.5 mA for 4 minutes and 5 mA for 6 minutes. The patients received an average of 2.5 treatments. Responses were graded according to the following criteria: active range of motion, ability to exercise muscle strength with the use of the involved joint, girth measurement, performance of functional activities, and subjective relief. The patients derived

Table IV. *Cont'd*

Reference	Chemical	No.*	Current and time	Regimen	Results	Comments
	Glyco- or hexapyrronium bromide	27	Same as for tap water	As needed to achieve hypohidrosis	Mean duration of dryness: palms, 34 days; soles 47 days; axillae, 7 days	Uncontrolled study; prolonged hypohidrotic effect on palmar and 0.1% plantar skin
5	Tap water	NG	15-20 mA for 20-30 min	2-3 treatments per wk until euhidrotic	"Satisfactory"	Controlled study; untreated opposite side acting as control
11	Tap water	20	Adult, 15-20 mA for 20 min; child, 7-12 mA for 20 min	3 treatments per wk for 2 wk	Marked decrease in sweating of treated skin in both patient groups; no significant change in controls	Controlled study; 10 patients/10 controls; of each group (pt, control), half were treated on one side and half were treated bilaterally
52	Tap water		Both electrodes in same pan:	6 days per wk until euhidrotic	Treatments to achieve euhidrosis: Palms, 12 treatments; soles, 15 treatments; 5 mo of anhidrosis	Uncontrolled study; 30 total patients in study; no side effects; treatment effective regardless of polarity
		65	20 mA for 20 min			
		71	25 mA for 25 min		Palms, 13 treatments; soles, 21 treatments; 8.6 mo of anhidrosis	
			Electrodes in different pans:			
		5	10 mA for 15 min		Palms, 6 treatments; 8 mo of anhidrosis	
		62	10 mA for 25 min		Palms, 8 treatments; soles, 8 treatments; 3.4 mo of anhidrosis	

considerable benefit from the treatments. No relationship to sex or age was evident, but the shorter the time between the onset of the disease and the start of treatment, the greater the relief of symptoms.

Corticosteroid iontophoresis has been used successfully in Peyronie's disease (plastic induration of the penis).[48] Twelve patients with complaints of pain during intercourse, loss of rigidity of the penile shaft, and deviation of the penis during erection were treated with iontophoresis of hydrocortisone phosphate in a sodium carbonate solution with the use of a 4 to 8 mA current for 12 minutes three times weekly, for an average of twelve to thirteen treatments. Only one patient failed to show any improvement other than resolution of pain; the other eleven patients reported permanent relief from their respective complaints on follow-up examinations for periods of up to 29 months.

Hyperhidrosis. The most successful and popular application of iontophoresis for dermatologic conditions is the treatment of hyperhidrosis. In

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1936 it was noted that sweating could be reduced by ion transfer of certain solutions applied to the skin.* In 1948 iontophoresis was clearly shown to have an effect on sweat reduction.[49] The basic idea of such a treatment and practical aspects of the procedure are described by Grice,† Morgan,‡ and Levit.[50] Currently, tap water is the most commonly used conducting medium because it is effective and safe.[6,51,52] Solutions of various compounds have been investigated and anticholinergic compounds such as poldine methyl sulfate,[6,53] glycopyrronium bromide,[51] and atropine[54] were shown to have a longer lasting effect than water. However, side effects of systemic anticholinergic blockade prevented this form of treatment from gaining wide acceptance. Details of these studies are summarized in Table IV.

While the efficacy and safety of tap water iontophoresis is well documented, its mechanism of action remains unknown. The most widely accepted hypothesis is that sweating is inhibited by mechanical blockage of the sweat ducts at the stratum corneum level, the depth and severity of the damage being dose-related.[55,*,§] Stripping off the stratum corneum relieves the blockage and restores sweating.[56] More recent work by Hill et al[57] casts doubt on this theory. They examined by light and electron microscopy sweat glands from the palm of a patient with hyperhidrosis before and after treatment and found no changes.

Anesthesia. Early in the century, iontophoretic introduction of anesthetics such as cocaine, carbaine, and morphine was explored but only carbaine showed real promise.[21] More recently, iontophoresis of local anesthetics has been used by otolaryngologists for anesthesia of the middle ear.[58-64] Also, dentists have used iontophoresis for the anesthesia of oral mucosa.[65,66,‖] Gangarosa[12] reported extraction of twelve deciduous teeth with the use, only 5 to 15 minutes, of 2% lidocaine and epinephrine iontophoresis for anesthesia. In a separate controlled study Gangarosa[67] reported on anesthesia of the skin with the use of a variety of positive and negative controls, including iontophoresis of saline solution, topical application and iontophoresis of epinephrine and lidocaine separately, and topical administration of lidocaine and epinephrine. Skin anesthesia was best obtained with solutions containing 1% and 4% lidocaine and between 1/10,000 and 1/50,000 epinephrine. None of the control solutions were effective in producing anesthesia. He also reported no advantage in increasing lidocaine concentration from 2% to 4% and did not discern any difference between the lidocaine-epinephrine solution at a given concentration with and without a small amount of sodium chloride. He also found iontophoretic application of lidocaine with epinephrine for 3 to 5 minutes, using 1 mA, to be effective for preinjection topical anesthesia.

A special form of iontophoretic introduction of an "anesthetic" is fluoride treatment of exposed hypersensitive dentin.[68-73,*] Iontophoresis of anesthetics has not been used by dermatologists, but it may be worth considering, especially for pediatric patients.

Miscellaneous. Encouraging results in the treatment of vitiligo were obtained with the use of iontophoresis of 1% solution of meladine to eighteen patients.[74] The results were correlated with patient compliance: approximately twenty regularly spaced treatments for 10 to 15 minutes twice a week with a current of 3 to 5 mA were required for satisfactory results.

An attempt at treatment of scleroderma via iontophoresis of hyaluronidase was reported by Popkin,[75] who administered hyaluronidase in an acetate buffer solution to two patients, 3 to 15 mA for 5 to 15 minutes over 3 months. These patients experienced clinical improvement manifested by increased softness and flexibility of the tissues, decreased sensitivity to cold, improvement in skin

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color, and return of general well-being. Upon termination of therapy malaise and cold sensitivity returned in 1 week, but improvement in tissue softness, flexibility, and skin color persisted for up to 3 months.

Hyaluronidase iontophoresis has also been used in the treatment of lymphedema of the upper and lower extremities of varied etiology.[76] Control treatments were administered initially, followed by hyaluronidase iontophoresis, 20 mA for 20 to 30 minutes. In four of five patients the reduction in volume of the treated extremity was progressive and was maintained by simple elastic bandage compression. The refractory patient was noncompliant, apparently not wearing constricting support during the intervals.

Haxthausen[77] used iontophoretic technics to study the influence of various physical and chemical agents on allergic eczematous dermatitis (Table II). Wahlberg[20] reported encouraging results in the use of iontophoresis as a complement to ordinary patch testing in the investigation of obscure cases of contact eczema (Table II). With iontophoresis the test substances are administered rapidly and they migrate through the epidermis down into the dermis. Additionally, the disadvantages of the traditional patch test procedure, such as prolonged wearing of the test strips, are eliminated.

Other applications of the technic include iontophoretic introduction of "artificial skin pigment" (iron oxide and titanium oxide) into skin dermabraded for tattoo removal,[78] iodine iontophoresis to reduce scar tissue,[79] iontophoretic administration of antibiotics (penicillin) in burn patients,[80,81] and treatment of ear chondritis.[82]

Iontophoresis has also been found useful in the diagnosis of cystic fibrosis via sweat test.[83-89] Iontophoresis of pilocarpine has been approved by the FDA for this purpose and is widely used by pediatricians. Insulin delivery by this same route for cystic fibrosis patients has also been tested.[90,91]

Nondermatologic applications of iontophoresis are widely diversified. Some examples include acetic acid iontophoresis into joints for calcium deposits,[92] magnesium sulfate iontophoresis in the treatment of deltoid bursitis,* calcium iontophoresis in suspected myopathy,[93] histamine iontophoresis in the treatment of fibrosis and neuritis,[26] fluorescein penetration of the cornea[94] and other applications in investigative ophthalmology,[43,95,*] administration of vasodilators for peripheral vascular disease,[96] and other studies on blood vessel responses to iontophoretic administration of drugs.[97-100,†] Iontophoretic drug delivery, including antibiotic iontophoresis for the treatment of chronic adnexitis[101] and a traditional Chinese drug in female infertility,[102] has been used by gynecologists.[101,102,‡] The technic of microiontophoresis is used by neuroscientists for a wide spectrum of applications.[103-108]

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CONCLUSIONS

The technic of iontophoresis has been explored for many dermatologic and other medical conditions and considerable success has been achieved. In many cases, however, these explorations have been limited to a single clinical trial. More quantitative studies are needed to investigate potential applications to which this mode of therapy lends itself. Systematic approaches, including investigation of the basic science aspects of this technic, its mechanism of action, and case-controlled clinical studies, may lead to wider and more effective use of this versatile, yet safe and simple, therapeutic modality, especially in conditions that are refractory to the present armamentarium.

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ABSTRACTS

Lethal outbreak f hepatitis B in a dental practice

Shaw PE Jr, Barrett CL, Hamm R, et al: JAMA **255:**3260-3264, 1986

Nine symptomatic and fifteen asymptomatic patients (two deaths) with hepatitis B in rural Indiana were infected by a dentist whose serum was positive for hepatitis B surface antigen and hepatitis B e antigen. The dentist did not routinely wear gloves when treating patients. This is the eighth reported outbreak of hepatitis B traced to a dentist or an oral surgeon. On learning that he was a hepatitis B carrier the dentist discontinued his practice.

J. Graham Smith, Jr., M.D.

Hepatitis B associated with jet gun injection—California

Gregg MB: MMWR **35:**373-376, 1986

Thirty-one cases of hepatitis B were identified in attendees at a weight reduction clinic where treatment included daily parenteral injections of human gonadotropin given by jet injector. This is the first reported outbreak in which the jet injector has been implicated as the vehicle of transmission for hepatitis B.

J. Graham Smith, Jr., M.D.

Treatment of mycosis fungoides with isotretinoin

Fitzpatrick JE, Mellette JR: J Dermatol Surg Oncol **12:**626-629, 1986

A 56-year-old man with a 7-year history of mycosis fungoides was treated with a 6-month course of isotretinoin, 80 mg (1.0 mg/kg) per day for 6 months, with total clearing. While all patients with mycosis fungoides do not respond to isotretinoin, 16 of 21 in one series and 9 of 18 in another had some response.

J. Graham Smith, Jr., M.D.

Conservative outpatient management of ingrowing toenails

Senapati A: J R Soc Med **79:**339-340, 1986

Seventy-nine percent of twenty-five patients with ingrowing toenails treated conservatively by inserting cotton under the ingrowing nail edge were relieved of their symptoms after follow-up for a mean of 23.7 weeks. Conservative management is an effective low-cost method for treatment of these patients.

J. Graham Smith, Jr., M.D.