

BOTULINUM TOXIN A FOR AXILLARY HYPERHIDROSIS (EXCESSIVE SWEATING)

MARC HECKMANN, M.D., ANDRÉS O. CEBALLOS-BAUMANN, M.D., AND GERD PLEWIG, M.D.,
FOR THE HYPERHIDROSIS STUDY GROUP*

ABSTRACT

Background Treatment of primary focal hyperhidrosis is often unsatisfactory. Botulinum toxin A can stop excessive sweating by blocking the release of acetylcholine, which mediates sympathetic neurotransmission in the sweat glands.

Methods We conducted a multicenter trial of botulinum toxin A in 145 patients with axillary hyperhidrosis. The patients had rates of sweat production greater than 50 mg per minute and had had primary axillary hyperhidrosis that was unresponsive to topical therapy with aluminum chloride for more than one year. In each patient, botulinum toxin A (200 U) was injected into one axilla, and placebo was injected into the other in a randomized, double-blind manner. (The units of the botulinum toxin A preparation used in this study are not identical to those of other preparations.) Two weeks later, after the treatments were revealed, the axilla that had received placebo was injected with 100 U of botulinum toxin A. Changes in the rates of sweat production were measured by gravimetry.

Results At base line, the mean (\pm SD) rate of sweat production was 192 ± 136 mg per minute. Two weeks after the first injections the mean rate of sweat production in the axilla that received botulinum toxin A was 24 ± 27 mg per minute, as compared with 144 ± 113 mg per minute in the axilla that received placebo ($P < 0.001$). Injection of 100 U into the axilla that had been treated with placebo reduced the mean rate of sweat production in that axilla to 32 ± 39 mg per minute ($P < 0.001$). Twenty-four weeks after the injection of 100 U, the rates of sweat production (in the 136 patients in whom the rates were measured at that time) were still lower than base-line values, at 67 ± 66 mg per minute in the axilla that received 200 U and 65 ± 64 mg per minute in the axilla that received placebo and 100 U of the toxin. Treatment was well tolerated; 98 percent of the patients said they would recommend this therapy to others.

Conclusions Intradermal injection of botulinum toxin A is an effective and safe therapy for severe axillary hyperhidrosis. (N Engl J Med 2001;344:488-93.)
Copyright © 2001 Massachusetts Medical Society.

IN humans, sweating is induced by heat or exercise and is part of thermoregulation.¹ Primary hyperhidrosis is defined as excessive, uncontrollable sweating without any discernible cause. It most commonly involves the axillae, palms, and soles.² Severely affected patients have skin maceration and secondary microbial infections; their clothes may be drenched, especially from axillary hyperhidrosis; and they may be socially stigmatized. The diagnosis is

based on the patient's history and visible signs of excessive sweating. The extent of hyperhidrosis can be measured gravimetrically as the rate of sweat production (expressed in milligrams per minute).³⁻⁵

Therapies that have been shown to reduce the rate of sweat production include iontophoresis,³ topical application of aluminum chloride,⁶ and administration of anticholinergic agents and beta-blockers.⁷ For axillary hyperhidrosis, however, iontophoresis is cumbersome: several times a week, wet sponges wrapped around metal electrodes must be inserted into each armpit for 20 minutes and a low-voltage current applied to the skin, producing a stinging sensation. Application of aluminum chloride often must be discontinued because of skin irritation. Anticholinergic agents and beta-blockers may have substantial side effects.²

In certain instances, the surgical removal of sweat glands may be considered.^{8,9} Sympathectomy is of limited benefit for isolated axillary hyperhidrosis.¹⁰⁻¹³ Recently, the intradermal injection of botulinum toxin A has been shown to be effective in patients with gustatory sweating (pathologic sweating in response to the tasting of food, also known as Frey's syndrome)¹⁴ and those with axillary sweating,^{5,15-17} palmo-plantar sweating,^{4,18} or compensatory sweating (sweating in a circumscribed area because of lack of sweating in other areas).¹⁹ Botulinum toxin A blocks neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons.²⁰ It has been used extensively for decreasing muscle tone in patients with focal dystonia,²¹ spasticity,²² achalasia,²³ or chronic anal fissures.²⁴ Data on its use for hyperhidrosis are restricted to reports on small series of patients at specialized centers.^{4,5,16,17,25} We conducted a multicenter trial of botulinum toxin A in patients with axillary hyperhidrosis.

METHODS**Patients**

The study was conducted between January 1999 and March 2000. It was approved by the ethics committee of Ludwig Maximilians University (Munich, Germany) as well as the ethics committees of the participating medical centers. Patients were selected according to the following criteria: excessive axillary perspiration for more than one year; a rate of sweat production greater than 50 mg per minute on at least two occasions, as measured by a standardized

From the Department of Dermatology, Ludwig-Maximilians-Universität (M.H., G.P.), and the Department of Neurology, Technische Universität München (A.O.C.-B.) — both in Munich, Germany. Address reprint requests to Dr. Heckmann at Dermatologische Klinik, Ludwig-Maximilians-Universität, Frauenlobstr. 9-11, 80337 Munich, Germany, or at heckmann@derma.med.uni-muenchen.de.

*Other members of the Hyperhidrosis Study Group are listed in the Appendix.

gravimetric procedure; and failure of 10 percent or 20 percent solutions of topical aluminum chloride, applied daily before bed for four weeks, to control sweating. Exclusion criteria were the presence of neuromuscular disease; organic causes of hyperhidrosis, such as hyperthyroidism; concomitant therapy for hyperhidrosis; intake of drugs that may affect muscle tone or the autonomic nervous system; pregnancy; and cancer. All the patients provided written informed consent.

After enrollment, the patients underwent gravimetric assessments on two separate occasions before treatment was to begin. We initially enrolled 158 patients. Twelve of these patients were excluded after the second gravimetric assessment because they did not meet the inclusion criteria (in most cases, because their rate of sweat production was lower than the required rate); one of these patients had elevated serum levels of thyroid hormone. One additional patient withdrew from the study because he moved to a distant location. In total, we studied 145 patients from 24 centers, all of whom completed 14 weeks of follow-up; 136 patients completed 26 weeks of follow-up.

Measurement of Sweat Production

Gravimetric measurements were performed, as described previously,⁵ on at least two occasions before treatment and at every subsequent visit. Measurements were made after the patient had rested for 15 minutes at a room temperature of 21°C to 25°C. Briefly, filter paper (Melitta, Minden, Germany) was weighed on a high-precision laboratory scale (accuracy, ±0.5 mg) (Sartorius, Hamburg, Germany), placed in the armpits for 60 seconds, and then weighed again. The rate of sweat production (in milligrams per minute) was then calculated. Before treatment, the actively sweating areas were determined by means of Minor's iodine-starch test²⁶ and then outlined with a waterproof marker. Ten evenly distributed points within in each area were then marked as prospective sites for injection.

Study Design and Randomization

The sponsor of the study, Ipsen-Pharma (Ettlingen, Germany), supplied botulinum toxin A (Dysport) but did not design the study; did not collect, analyze, or interpret the data; and did not write any part of this report. Units of botulinum toxin A in this report refer specifically to the Dysport preparation and are not identical to the units used in other preparations of botulinum toxin A.

The first dose of botulinum toxin A (200 U) was injected intradermally into one axilla and placebo was injected into the other axilla in a randomized, double-blind fashion, as follows. For each patient, two vials, each labeled either "right axilla" or "left axilla," were prepared by Penn Pharmaceuticals Clinical Studies Supply Unit (Gwent, United Kingdom) according to a computerized randomization scheme. One vial contained botulinum toxin A (500 U, stabilized with 0.125 mg of human albumin and 2.5 mg of lactose), and the other contained placebo (0.125 mg of human albumin and 2.5 mg of lactose); they were prepared as identical lyophilized pellets. The treating physician dissolved the pellet contained in each vial in 5 ml of 0.9 percent sodium chloride solution and injected 10 0.2-ml fractions of the resulting solution (a total of 200 U of botulinum toxin A or placebo) into the respective axilla. Neither the treating physician nor the patient knew which axilla received botulinum toxin A and which received placebo. The treatment-allocation code for each patient was kept in a sealed envelope and revealed on day 14 after the injections, after the treatment results had been evaluated gravimetrically. The contents of a third vial, labeled "second injection," which contained 500 U of botulinum toxin A, was then dissolved in 5 ml of sterile sodium chloride, and 10 0.1-ml fractions of the resulting solution (for a total of 100 U of botulinum toxin A) were then injected into the axilla that had previously been treated with placebo.

Questionnaire

On day 28 after the injection of 200 U of botulinum toxin A or placebo, patients were asked the following questions: Are you sat-

isfied with this treatment (completely satisfied, satisfied, partially satisfied, or not satisfied)? How would you describe your tolerance of this treatment (excellent, good, fair, or poor)? Would you recommend this treatment to others (in all cases, in most cases, in some cases, or not at all)?

Statistical Analysis

Statistical analysis was performed with the SAS software package (version 6.12, SAS Institute, Cary, N.C.). Absolute values for the rate of sweat production were the primary outcome. The rate of sweat production in one axilla was compared with that in the other with use of paired t-tests.²⁷ The relative reduction in sweating was computed as the percentage difference between the pretreatment (base-line) and post-treatment rates of sweat production; for instance, a change in the rate of sweat production from 160 mg per minute to 40 mg per minute was a 75 percent reduction. The Wilcoxon-Mann-Whitney test²⁷ was used to compare the reduction in sweat production after the injection of 200 U of botulinum toxin A with the reduction after the injection of 100 U. The McNemar test²⁷ was used for pairwise comparisons of 200 U and 100 U of botulinum toxin A and placebo with respect to rates of response and treatment failure. All statistical tests were two-sided. The analysis was based on data for all patients who received both doses of botulinum toxin A.

RESULTS

The base-line characteristics of the 145 patients who completed 14 weeks of follow-up are summarized in Table 1. Gravimetrically measured rates of sweat production ranged from 50 to 1000 mg per minute (mean, 192±136; median, 154), but the mean difference between the rates in the two axillae in the same person was 12±71 mg per minute. Men had a higher rate of sweat production than women (208±117 vs. 174±119 mg per minute, P=0.01). Age, body-mass index, smoking status, and the presence or absence of atopic diseases were not associated with sweat production. The mean rates of sweat production at base line were 165 mg per minute in the axillae assigned to

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 145 PATIENTS WHO COMPLETED 14 WEEKS OF FOLLOW-UP.*

VARIABLE	VALUE
Age (yr)	31.8±11.0
Sex (M/F)	76/69
Smoking status†	
Smoker	60
Nonsmoker	85
Body weight (kg)	72.8±14.2
Body-mass index‡	23.8±3.4
Size of hyperhidrotic area (cm ²)	48.5±25.4
Rate of sweat production (mg/min)	192±136

*Plus-minus values are means ±SD.

†Smoking status was reported by the patients at the time of enrollment.

‡Body-mass index is the weight in kilograms divided by the square of the height in meters.

treatment with botulinum toxin A and 174 mg per minute in the axillae assigned to placebo ($P=0.15$).

Two weeks after the initial injections, the mean rates of sweat production were 24 ± 27 mg per minute in the axillae treated with botulinum toxin A and 144 ± 113 mg per minute in the axillae treated with placebo (mean difference between the groups, 111 mg per minute; 95 percent confidence interval, 91 to 132; $P<0.001$) (Fig. 1). The decrease from base line of 30 mg per minute in the rate of sweat production in the axillae treated with placebo was also significant ($P=0.004$). In 142 of the 145 patients (98 percent), the reduction in sweating was greater in the axilla treated with botulinum toxin A.

Two weeks after the injection of 100 U of botulinum toxin A into the axillae that had initially been treated with placebo, the mean rate of sweat production had decreased from 144 ± 113 to 32 ± 39 mg per minute ($P<0.001$) (Fig. 1). Twelve and 24 weeks after the 100-U injection, there were gradual increases in sweat production. The mean reduction in sweating two weeks after treatment with botulinum toxin A was 76.5 percent with 100 U, as compared with 81.4 percent with 200 U ($P=0.04$). When the two doses were compared in the 145 individual patients, 3 (2.1 percent) had equal reductions in sweating with the two doses, 64 (44.1 percent) had a greater reduction

in sweating with 100 U, and 78 (53.8 percent) had a greater reduction with 200 U. Comparisons based on additional criteria and defined according to absolute or percentage reductions in sweating are shown in Table 2. Twenty-four weeks after the injection of 100 U of botulinum toxin A, the rates of sweat production (in the 136 patients in whom the rates were measured at that time) were still lower than the baseline values: 67 ± 66 mg per minute in the axillae that had received 200 U and 65 ± 64 mg per minute in the axillae that had received placebo and 100 U.

During the first 14 weeks of follow-up, no major adverse events were associated with treatment with botulinum toxin A. Temporary adverse effects included headache in four patients, muscle soreness of the shoulder girdle in two, increased facial sweating in one, and axillary itching in one. At four weeks after the initial injections, 118 patients (81.4 percent) rated their tolerance of treatment as excellent, 25 (17.2 percent) rated it as good, and 2 (1.4 percent) rated it as fair. Ninety-two patients (63.4 percent) reported that they were completely satisfied, 42 (29.0 percent) reported that they were satisfied, and 11 (7.6 percent) reported that they were partially satisfied; no one said that he or she was not satisfied. When asked whether they would recommend this treatment to others, 126 patients (86.9 percent) said that they would recommend

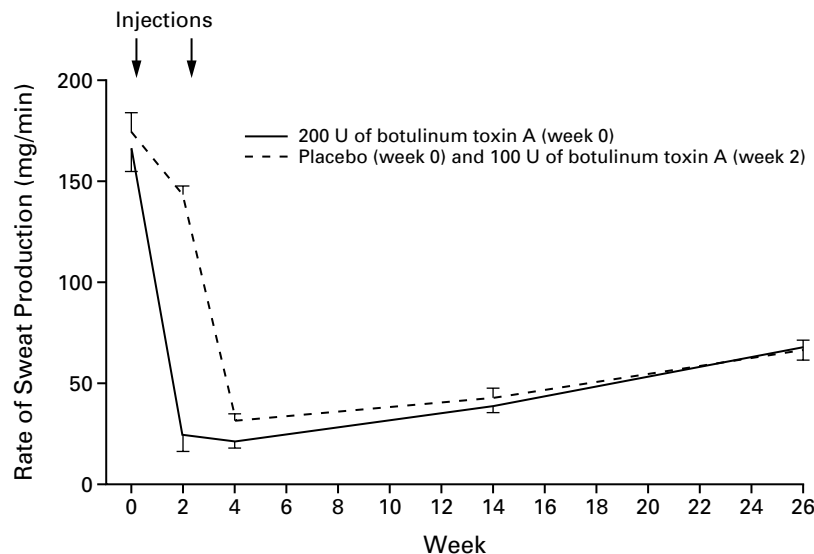


Figure 1. Mean (\pm SE) Rates of Sweat Production after Intradermal Injection of Botulinum Toxin A or Placebo.

At week 0, 200 U of botulinum toxin A was injected into one axilla in each patient and placebo into the other. At week 2, 100 U of botulinum toxin was injected into the axilla that had received placebo. Data were available for 145 patients at week 14 and for 136 at week 26. For the axillae that received 200 U of botulinum toxin A, the rate differed significantly ($P<0.001$) from the base-line rate throughout follow-up. For the axillae that initially received placebo, the value differed significantly from base line at week 2 ($P=0.004$); the changes from base line were also significant at weeks 4, 14, and 26, after the injection of 100 U of botulinum toxin A ($P<0.001$). Paired t-tests were used for all comparisons.

TABLE 2. RATE OF SWEAT PRODUCTION AND OUTCOMES TWO WEEKS AFTER TREATMENT WITH BOTULINUM TOXIN A OR PLACEBO.*

VARIABLE	200 U OF BOTULINUM TOXIN A	100 U OF BOTULINUM TOXIN A	PLACEBO
	no. of axillae (%)		
Rate of sweat production			
≤50 mg/min	126 (86.9)	120 (82.8)	7 (4.8)
≤25 mg/min	94 (64.8)	90 (62.1)	2 (1.4)
0 mg/min	7 (4.8)	10 (6.9)	0
Reduction in sweating			
≥25%	138 (95.2)	138 (95.2)	50 (34.5)
≥50%	134 (92.4)	129 (89.0)	22 (15.2)
≥75%	114 (78.6)	99 (68.3)	4 (2.8)
Combined outcomes			
≥25% and ≤50 mg/min	126 (86.9)	119 (82.1)	5 (3.4)
<25% and >50 mg/min	7 (4.8)	6 (4.1)	93 (64.1)

*P<0.001 for all comparisons between 200 U of botulinum toxin A and placebo and between 100 U of botulinum toxin A and placebo. P>0.1 for all comparisons between 200 U and 100 U except for the number of patients with a 75 percent reduction in sweating (P=0.03). The McNemar test was used for all comparisons.

it in all cases, 16 (11.0 percent) that they would recommend it in most cases, and 2 (1.4 percent) that they would not recommend it; 1 patient (0.7 percent) did not respond to this question.

DISCUSSION

Hyperhidrosis, although it is not life-threatening, can have a substantial effect on the quality of life. Our multicenter study provides evidence of the efficacy and safety of intradermal botulinum toxin A injections in reducing focal axillary hyperhidrosis. We chose to use gravimetry to monitor the effects of treatment, since this method yields objective data and is easily reproducible. Other methods, such as the iodine–starch test²⁶ or other staining procedures,²⁸ are only semi-quantitative.

Water-vapor analysis performed with the use of a detector over a flat skin surface after the injection of methacholine, the most accurate method of measuring maximal sweat production,²⁹ is not feasible in the axillae. We are unaware of any representative epidemiologic data on what might be considered a normal rate of sweat production; an arbitrary definition of palmar hyperhidrosis as a rate of sweat production greater than 20 mg per minute according to gravimetric measurements has been proposed.³⁰ We chose axillary rates of sweat production greater than 50 mg per minute to select patients with clinically evident axillary hyperhidrosis.

Our study confirms and extends the results of previous studies, which were limited to small series of patients treated in specialized institutions with diverse protocols.^{4,5,15-17} In our study, although the difference

in outcomes between placebo and botulinum toxin A treatment was obvious, there was also a significant decrease in the mean rate of sweat production in the axillae treated with placebo. In statistical terms, this is readily explicable by regression to the mean in measurements obtained after we had selected a threshold value of sweat production. Since the injections of placebo and of 200 U of botulinum toxin A were given on the same occasion, it is possible that the axilla injected with placebo benefited from the contralateral injection as a result of the systemic spread of botulinum toxin A. Subclinical changes in the activity of distant muscles have been observed after intramuscular injection of botulinum toxin A for the treatment of dystonia.^{31,32} However, studies in which 400 U of botulinum toxin A (twice the dose we used in this study) was administered to only one axilla did not show any improvement in the untreated axilla according to gravimetry.^{5,16} Thus, subclinical spread of botulinum toxin A is an unlikely explanation for measurable changes in rates of sweat production.

Detailed dose–response curves for botulinum toxin A have not been established either for the treatment of hyperhidrosis or for most other clinical uses of this drug. Botulinum toxin A is available in the United States as Botox (manufactured by Allergan, Irvine, Calif.) and in Europe as Botox or Dysport (manufactured by Ipsen Biopharm, Wrexham, United Kingdom). In terms of clinical efficacy in humans, 1 U of Botox is estimated to be equal to 3 to 4 U of Dysport, the product used in our study.^{20,33,34} On the basis of previously reported clinical experience,^{5,16} 200 U of botulinum toxin A (Dysport), divided into 10 fractions, was chosen as the dose most likely to produce a satisfactory effect. We found little difference in the treatment effect seen with 200 U (81.4 percent reduction in sweat production) and that seen with 100 U (76.5 percent reduction). Comparison of the results two weeks after the initial injections must be interpreted cautiously, because of the effect of the placebo injections. The reductions in the rate of sweat production at four weeks (two weeks after the injection of 100 U of botulinum toxin A into the axillae that had received placebo), however, were similar in the two axillae. Follow-up measurements of the rates of sweat production showed no advantage to the higher dose.

For sustained relief from symptoms of hyperhidrosis, additional injections of botulinum toxin A at varying intervals are usually required. There are no explicit criteria for the dose and frequency of the subsequent treatments; according to previous reports, patients have requested additional injections 4 to 17 months after the first treatment.^{4,5,16,17,35,36} We found that although the mean rate of sweat production gradually increased after injection of botulinum toxin A, after six months it was still well below half the initial mean rate. The exact mechanisms of recurrent hyperhidrosis

after intradermal injection of botulinum toxin A are unknown. It has been consistently shown that new nerve endings grow within three months after intramuscular injection of botulinum toxin A³⁷; however, sympathetic nerve endings that innervate the sweat glands have not been studied. Resistance to botulinum toxin A occurs in up to 5 percent of patients with dystonia³⁸ and has been attributed to the induction of antibodies against botulinum toxin A. We did not observe resistance to botulinum toxin A in our study, nor are we aware that has it been observed in other studies of patients with hyperhidrosis.

We conclude that intradermal injection of botulinum toxin A is a safe, effective, and well-tolerated treatment for axillary hyperhidrosis and should be considered for patients who do not have a response to topical treatment.

Supported by Ipsen-Pharma, Ettlingen, Germany. Dr. Heckmann and Dr. Ceballos-Baumann have received honorariums for speeches from Ipsen-Pharma and from other companies that manufacture botulinum toxin.

We are indebted to K. Dürrstein, Ph.D., C. Hautmann, M.D., and I. Mohr, Ph.D., for management; to D. Schremmer, Ph.D., for statistical analysis (at the Gesellschaft für Therapieforschung, Munich, Germany); and to B. Rzany, M.D., for valuable discussions.

APPENDIX

The Hyperhidrosis Study Group includes the following (listed in alphabetical order): Dermatologische Klinik, Krankenhaus Berlin-Spandau (G. Albrecht and A. Härtel); Klinik und Poliklinik für Dermatologie, Rheinische Friedrich-Wilhelms-Universität, Bonn (T. Bieber, R. Gersden, and W. Petrow); Hautklinik, Städtische Kliniken Dortmund (U. Beiteke, P.J. Frosch, and A. Magerl); Klinik und Poliklinik für Dermatologie, Carl Gustav Carus Universität, Dresden (G. Sebastian and A. Stein); Hautklinik der Heinrich-Heine-Universität, Düsseldorf (A. Humke and T. Ruzicka); Zentrum der Dermatologie und Venerologie, Johann-Wolfgang-Goethe-Universität, Frankfurt (J. Gille, R. Kaufmann, and K. Spieth); Universitäts-Hautklinik, Albert-Ludwigs-Universität, Freiburg (M. Peschen and W. Vanscheidt); Zentrum für Dermatologie und Andrologie, Universitätsklinikum Giessen (M. Eberl and W.B. Schill); Universitäts-Hautklinik, Göttingen (K. Kölmel and S. Fischer); Hautklinik, Allgemeines Krankenhaus St. Georg, Hamburg (A. Kirchhoff); Hautklinik der Ruprecht-Karls-Universität, Heidelberg (D. Petzoldt and M. Richter); Universitätsklinik des Saarlandes, Hautklinik und Poliklinik, Homburg/Saar (D. Dill-Müller and V. Nuber); Hautklinik, Städtische Kliniken Kassel (W. Prager, R. Rompel, and S. Scholz); Klinik und Poliklinik für Dermatologie und Venerologie, Universität zu Köln (C. Sacher); Klinik und Poliklinik für Hautkrankheiten, Universität Leipzig (B. Haupt, U.F. Haustein, and P. Nenoff); Klinik für Dermatologie und Venerologie, Universitätsklinikum Lübeck (M. Hantschke and H.H. Wolff); Klinik und Poliklinik für Dermatologie und Venerologie, Otto-von-Guericke-Universität Magdeburg (H. Gollnick and M. Krause); Klinik für Dermatologie, Allergologie, und Venerologie, Klinikum Mannheim (G. Feller and B. Rzany); Klinik und Poliklinik für Dermatologie und Allergologie, Ludwig-Maximilians-Universität, München (S. Breit, M. Dendorfer, G. Kick, M. Schaller, and B. Wörle); Klinik und Poliklinik für Dermatologie, Universität Regensburg (S. Karrer and R.M. Szeimies); Klinik und Poliklinik für Dermatologie und Venerologie, Universität Rostock (B. Ehlers and G. Gross); Universitäts-Hautklinik, Ulm (P. Gottlöber, R.U. Peter, and M. Steinert); Klinik und Poliklinik für Haut- und Geschlechtskrankheiten, Universität Würzburg (H. Hamm and S. Rickert); and Dermatologische Klinik, Universitätsspital Zürich (R. Böni, G. Burg, B. Heidecker, and O. Kreyden).

REFERENCES

- Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. *J Am Acad Dermatol* 1989;20:537-63.
- Idem*. Biology of sweat glands and their disorders. II. Disorders of sweat gland function. *J Am Acad Dermatol* 1989;20:713-26.
- Reinauer S, Neusser A, Schauf G, Holzle E. Iontophoresis with alternating current and direct current offset (AC/DC iontophoresis): a new approach for the treatment of hyperhidrosis. *Br J Dermatol* 1993;129:166-9.
- Naumann M, Hofmann U, Bergmann I, Hamm H, Toyka KV, Reiners K. Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. *Arch Dermatol* 1998;134:301-4.
- Heckmann M, Breit S, Ceballos-Baumann A, Schaller M, Plewig G. Side-controlled intradermal injection of botulinum toxin A in recalcitrant axillary hyperhidrosis. *J Am Acad Dermatol* 1999;41:987-90.
- Shelley WB, Hurley HJ Jr. Studies on topical antiperspirant control of axillary hyperhidrosis. *Acta Derm Venereol* 1975;55:241-60.
- Mack GW, Shannon LM, Nadel ER. Influence of beta-adrenergic blockade on the control of sweating in humans. *J Appl Physiol* 1986;61:1701-5.
- Freeman R, Waldorf HA, Dover JS. Autonomic neurodermatology. II. Disorders of sweating and flushing. *Semin Neurol* 1992;12:394-407.
- Lillis PJ, Coleman WP III. Liposuction for treatment of axillary hyperhidrosis. *Dermatol Clin* 1990;8:479-82.
- Byrne J, Walsh TN, Hederan WP. Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis. *Br J Surg* 1990;77:1046-9.
- Zacherl J, Huber ER, Imhof M, Plas EG, Herbst F, Fugger R. Long-term results of 630 thoracoscopic sympathectomies for primary hyperhidrosis: the Vienna experience. *Eur J Surg Suppl* 1998;580:43-6.
- Lai YT, Yang LH, Chio CC, Chen HH. Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. *Neurosurgery* 1997;41:110-3.
- Heckmann M. Complications in patients with palmar hyperhidrosis treated with transthoracic endoscopic sympathectomy. *Neurosurgery* 1998;42:1403-4.
- Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. *Acta Otolaryngol* 1995;115:459-61.
- Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin — a possible new treatment for axillary hyperhidrosis. *Clin Exp Dermatol* 1996;21:276-8.
- Heckmann M, Breit S, Ceballos-Baumann A, Schaller M, Plewig G. Axilläre Hyperhidrose: Erfolgreiche Behandlung mit Botulinumtoxin-A. *Hautarzt* 1998;49:101-3.
- Schnider P, Binder M, Kittler H, et al. A randomized, double-blind, placebo-controlled trial of botulinum A toxin for severe axillary hyperhidrosis. *Br J Dermatol* 1999;140:677-80.
- Schnider P, Binder M, Auff E, Kittler H, Berger T, Wolff K. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *Br J Dermatol* 1997;136:548-52.
- Heckmann M, Schaller M, Ceballos-Baumann A, Plewig G. Botulinum beyond wrinkles. *Dermatol Surg* 1997;23:1221-2.
- Hambleton P. Clostridium botulinum toxins: a general review of involvement in disease, structure, mode of action and preparation for clinical use. *J Neurol* 1992;239:16-20.
- Hallett M. One man's poison — clinical applications of botulinum toxin. *N Engl J Med* 1999;341:118-20.
- Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 1995;45:712-7.
- Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intraspinal botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995;332:774-8. [Erratum, *N Engl J Med* 1995;333:75.]
- Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med* 1999;341:65-9. [Erratum, *N Engl J Med* 1999;341:624.]
- Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis: no sweat Botox. *Dermatol Surg* 1998;24:817-9.
- Minor V. Ein neues Verfahren zu der klinischen Untersuchung der Schwerrabsorption. *Dtsch Z Nervenheilkd* 1928;101:302-7.
- Woolson RF. Statistical methods for the analysis of biomedical data. New York: John Wiley, 1987.
- Guttman L. A demonstration of the study of sweat secretion by the quinazarin method. *Proc R Soc Med* 1941;35:77-8.
- Sato K, Sato F. Variable reduction in beta-adrenergic sweat secretion in cystic fibrosis heterozygotes. *J Lab Clin Med* 1988;111:511-8.
- Reinauer S, Neusser A, Schauf G, Hölzle E. Die gepulste Gleichstrom-Iontophorese als neue Behandlungsmöglichkeit der Hyperhidrosis. *Hautarzt* 1995;46:543-7.
- Lange DJ, Brin ME, Warner CL, Fahn S, Lovelace RE. Distant effects of local injection of botulinum toxin. *Muscle Nerve* 1987;10:552-5. [Erratum, *Muscle Nerve* 1988;11:520.]
- Erbguth F, Claus D, Engelhardt A, Dressler D. Systemic effect of local botulinum toxin injections unmasks subclinical Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry* 1993;56:1235-6.

- 33.** Dressler D, Rothwell JC. Electromyographic quantification of the paralyzing effect of botulinum toxin in the sternocleidomastoid muscle. *Eur Neurol* 2000;43:13-6.
- 34.** Krack P, Deuschl G, Benecke R, et al. Dose standardization of botulinum toxin. *Mov Disord* 1998;13:749-51.
- 35.** Heckmann M, Schaller M, Ceballos-Baumann A, Plewig G. Follow-up of patients with axillary hyperhidrosis after botulinum toxin injection. *Arch Dermatol* 1998;134:1298-9.
- 36.** Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. *Dermatol Surg* 1998;24:1237-41.
- 37.** de Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A* 1999;96:3200-5.
- 38.** Siatkowski RM, Iyutyunikov A, Biglan AW, et al. Serum antibody production to botulinum A toxin. *Ophthalmology* 1993;100:1861-6.

Copyright © 2001 Massachusetts Medical Society.