Frey syndrome treatment with botulinum toxin

PAVEL DULGUEROV, MD, DIDIER QUINODOZ, MD, GRÉGOIRE COSENDAI, BS, PIERRE PILETTA, MD, and **WILLY LEHMANN, MD,**
Geneva, Switzerland

The goal of this work is to present our results of the intradermic infiltration with botulinum toxin in patients with Frey syndrome. Sixteen hemifaces in 15 patients were studied. Gustatory stimulation was evoked by sucking on a slice of lemon while measurements were done on both hemifaces, with the normal side being used as a control. Skin temperature and color (erythema) were measured with a digital surface thermometer and a skin chromameter, respectively. Sweat quantity and surface were measured by using the previously described blotting paper and iodine-sublimated paper histogram methods, respectively. Testing was repeated 2 weeks after skin infiltration with botulinum toxin (dilution of 50 U/mL). The interinjection distances were 1 cm, and 0.1 mL (5 U) was infiltrated at each injection site. Frey syndrome complaints disappeared in all patients. Small residual amounts of sweat were measurable. The difference in sweat quantity before and after botulinum toxin infiltration was significant in every patient ($P < 0.001$). Skin temperature and color measurement gave inconclusive results. In conclusion, Frey syndrome treatment with botulinum toxin is an efficient and well-tolerated technique. Further work should address the optimal injection parameters. (Otolaryngol Head Neck Surg 2000;122:821-7.)

Frey syndrome occurs several months to a few years after parotid surgery[1,2] and is characterized by facial sweating and flushing during meals. Although this syndrome has come to bear Lucie Frey's name,[3] it was first reported by Baillarger in 1853[4] and not by Duphenix,[5] as commonly cited.[6] A series of arguments, reviewed elsewhere, favor the so-called aberrant regeneration theory[7,8] as the physiopathologic explanation. The aberrant regeneration supposes that the parasympathetic fibers, which normally innervate the parotid gland after losing their parotid targets during parotidectomy, regenerate to innervate the facial skin vessels and sweat glands. The normal function of the parotid parasympathetic fibers is to increase salivary secretion during eating, and therefore their activation after aberrant regeneration produces a stimulation of the new targets during meals, resulting in a local vasodilatation *(gustatory flushing)* and localized sweating *(gustatory sweating)*. What is rarely realized is that in order for this aberrant regeneration to occur, the sympathetic fibers to facial skin vessels and sweat glands have to be damaged. This is a frequent event after either parotid surgery or penetrating parotid trauma but may also occur after cervical sympathectomy, another cause of Frey syndrome.[9,10]

Once present, Frey syndrome continues unabated without treatment.[1,2] Although Frey syndrome is probably an unavoidable aftereffect of parotidectomy,[1,11] only about half of the patients are symptomatic.[1,11] Among symptomatic patients, about half judge their symptoms as "important or embarrassing."[1] For these patients, different treatments have been attempted with limited success. These treatments can be classified into the following groups: (1) section of some portion of the efferent arc, such as the auriculotemporal nerve,[12-14] the intracranial portion of the glossopharyngeal nerve,[15] or the tympanic plexus in the so-called tympanic neurectomy[16,17]; (2) radiotherapy[18]; (3) local topical anticholinergics[19-21]; and (4) reoperation and placement of an interposition barrier.[22] All these techniques are either inefficient in the long run or have potential side effects that are worse than the symptoms they are supposed to treat. Therefore explanation and reassurance is commonly considered as the most adequate treatment for Frey syndrome.[23]

Recently, several studies[24,25] have described a new method for the treatment of Frey syndrome—the local infiltration of botulinum toxin in the involved skin. Botulinum toxin can be viewed as an anticholinergic, and this treatment is effective because the (normal sympathetic and regenerated parasympathetic) synapses on

From the Division of Head and Neck Surgery (Drs Dulguerov, Quinodoz, and Lehmann), the Cochlear Implants Center (Mr Cosendai), and the Clinic of Dermatology and Venerology (Dr Piletta), Geneva University Hospital.

Presented at the 84th Spring Meeting of the Swiss Otolaryngology–Head and Neck Surgery Society, Sankt Gallen, Switzerland, June 15, 1997, and the Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery, San Antonio, TX, September 12, 1998.

Reprint requests: Pavel Dulguerov, MD, Division of Head and Neck Surgery, Geneva University Hospital, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland.

0194-5998/2000/$12.00 + 0 **23/77/99738**
doi:10.1067/mhn.2000.99738

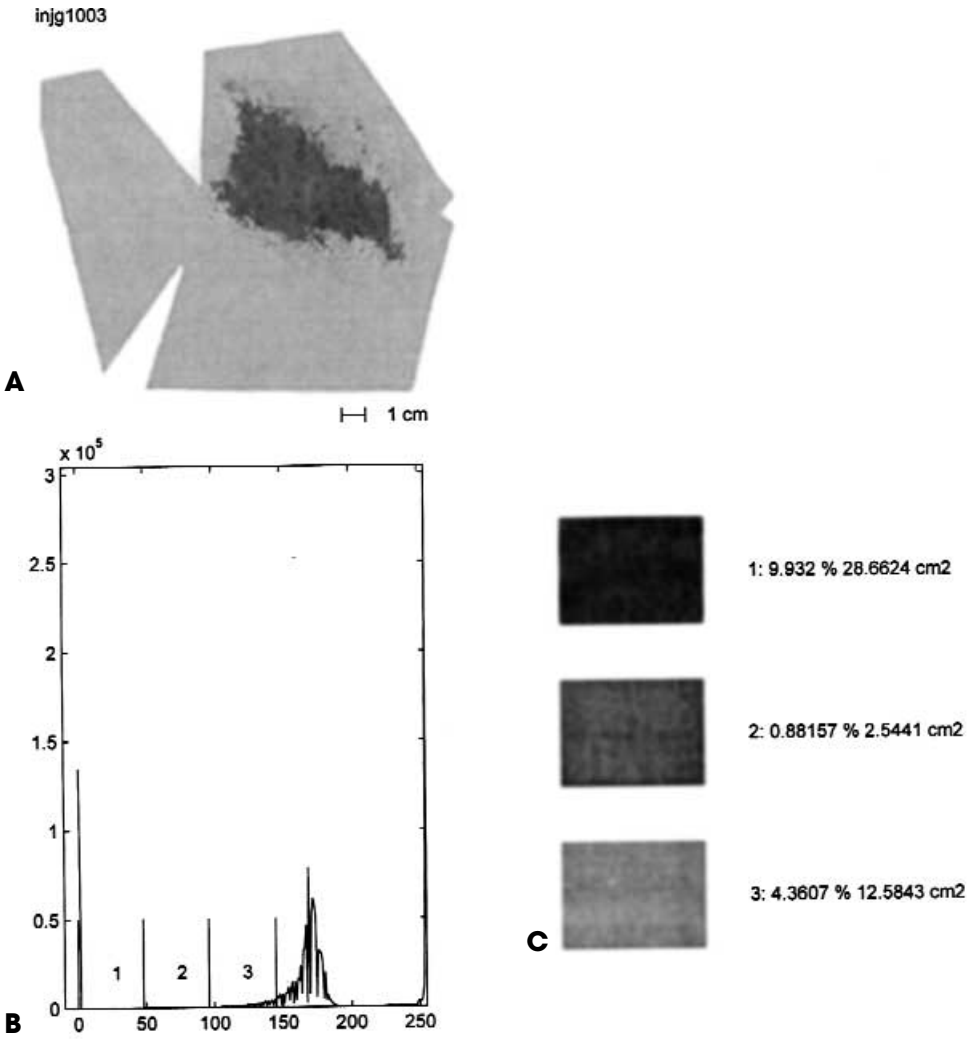

Fig 1. Data sheet from the IPSH method. The printout of the digitized stencil is shown **(A)**, as well as the gray scale histogram **(B)** and the relevant surfaces **(C)**. **A,** The shape of the stencil resembles a fish with several cuts: (1) a small cut (anteriorly) is made for the corner of the mouth, (2) a wide deep cut (superiorly) for the ear lobe, and (3) a narrow deep cut (inferiorly) located in the neck below the mandible that was necessary to prevent undue paper folding during testing. **B,** The histogram X-axis corresponds to the degree of darkness, with 0 being the darkest shade and 256 being the lightest shade. The threshold algorithm has set the amber color of the stencil background as 147. Three histogram bins of 49 units each are created: darkest *(1)*, intermediate darkness *(2)*, and low darkness *(3)*. **C,** Data for these 3 histogram bins with their surfaces in square centimeters and as a percentage of the total surface of the stencil. Only the value of the darkest bin (No. 1) is taken to represent wet paper and therefore used in further calculations.

cutaneous vessels and sweat glands are cholinergic[26,27] contrary to other sympathetic postganglionic synapses. Actually, the presence of an identical neurotransmitter (between the normal skin sympathetic innervation and the regenerating parotid parasympathetic fibers) is another requirement for an aberrant regeneration to occur.

We report our experience with this technique and the use of newly described methods[28] for the evaluation of facial gustatory sweating.

METHODS AND MATERIAL

Sixteen symptomatic Frey syndrome hemifaces in 15 patients (one patient with bilateral Frey syndrome) were included in the study. The principal complaint was intense sweating during eating. This sweating was present during each meal in 12 patients. In addition to gustatory sweating, 4 patients also noted a localized flushing during meals, which was never described as disturbing.

Gustatory stimulation was evoked when the patient sucked

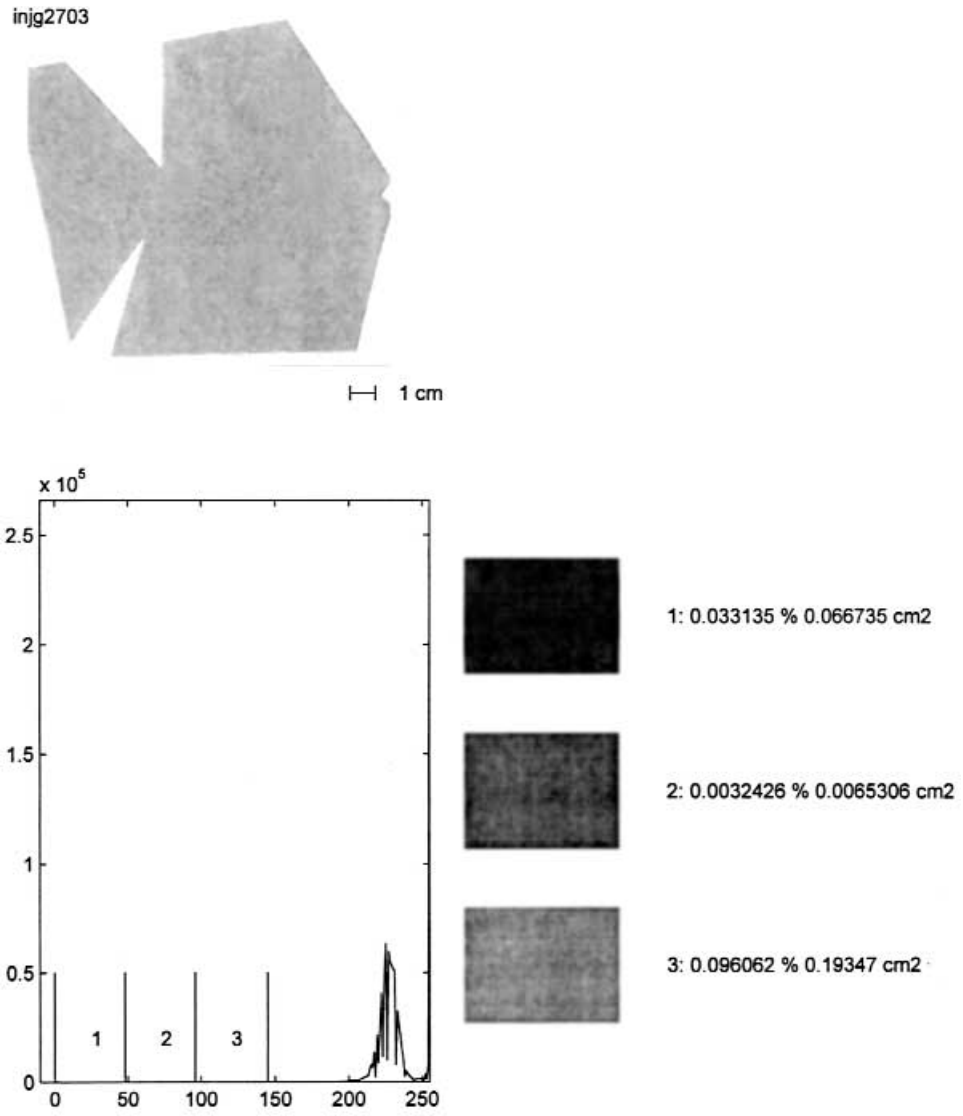

Fig 2. Data sheet from the ISPH method of the same patient as Fig 1, 2 weeks after infiltration of botulinum toxin.

on a slice of lemon. The lemon slice was placed in the mouth, and the patient was asked to gently suck on the slice without undue chewing. Measures were performed in a specially air-conditioned room (22°C ± 1°C, 25% ± 5% humidity) after 5 minutes of acclimatization of the patient. Most data were collected at the same time of the day (9-12 AM). Four parameters (skin temperature and color, sweating quantity, and surface) were measured during this gustatory stimulation on each hemiface, with the controlateral side being used as a control. Measures were taken on the day of the botulinum toxin infiltration and repeated 2 weeks later. Statistical comparison of the measures taken before and after botulinum toxin injection was performed with the bilateral Student *t* test by using the statistical algorithms of the SPSS 7.5 software (SPSS Inc, Chicago, IL).

The skin temperature was measured by using a digital contact thermometer (Digital Termometer TTX 1096; Ebro Electronic GmbH, Ingolstadt, Germany). The skin erythema was assessed with a digital chromameter (Minolta CR 300).

Sweat quantity and sweat surface were measured with the blotting paper (BP) and the iodine-sublimated paper histogram (ISPH) methods, respectively. Each method used a custom stencil (Fig 1, *A*) that was adapted to the rather complicated topology of the lateral facial area. In both methods the stencil was applied on both sides of the face during a gustatory stimulation for a duration of 1 minute. Technical details have been previously reported, as well as a calibration with known quantities of NaCl.[28] Briefly, the BP technique is a quantitative measure of the amount of sweat generated by

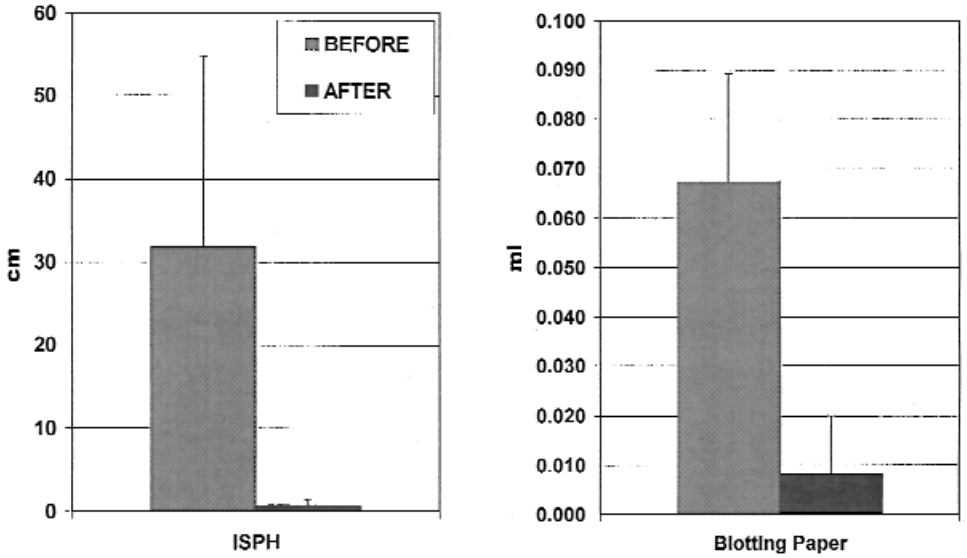

Fig 3. Left, Sweating surface, in square centimeters, measured by the ISPH method before and after treatment of Frey syndrome by the intradermal injection of botulinum toxin (average and SD). **Right,** Sweat quantity, in grams or milliliters, measured by the BP technique before and after treatment of Frey syndrome by the intradermal injection of botulinum toxin (average and SD).

measuring the weight change in a BP before and after the absorption of the sweat. The ISPH method is a modification of the classical Minor test.[29] Regular office paper sheets, which naturally contain various amounts of starch, have been sublimated with iodine, taking on an amber color. Wetting this paper results in a localized color change from amber to blue, corresponding to the reduction of starch by water, which is similar to color changes of the Minor iodine-starch mixture. The colored paper sheet was scanned in an 8-bit grayscale mode, and the digital image was subjected to a histogram algorithm. Because the stencils were scanned in an 8-bit mode, the available range of darkness is from 0 to 256 (X-axis, Fig 1*B*). A threshold was applied to eliminate the clear amber tones of the stencil background (value 147; Fig 1*B*). The remaining histogram data were divided into 3 bins of equal width, corresponding to increasing darkness. The darkest bin (No. 1; Fig 1*B* and *C*) corresponds to paper zones in which the starch is supposed to be totally reduced by the applied water (sweat), and only the surface of this darkest bin was taken into account to evaluate the wet surface.[28]

After mapping the surface involved by Frey syndrome with the ISPH stencils, botulinum toxin (5 U per 0.1 mL) was injected intradermally with a 30-gauge needle. Injection sites were about 1 cm apart, and each received about 0.1 mL (5 U) of botulinum toxin. We also asked patients to evaluate the pain of injection by using a 10-cm visual analogous scale.

RESULTS

Subjectively, facial sweating and flushing during meals disappeared in all patients after botulinum toxin injection. The pain of the intradermal injection was evaluated as 2.5 ± 1.2 on a scale from 0 to 10.

The total doses used for each patient varied from 0.3 to 1.5 mL or 15 to 75 U. No secondary side effects were reported by the patients or noticed by the investigators.

The results for skin temperature and color were not conclusive; that is, there was not a clear difference before and after injection with botulinum toxin. For the patients presenting a gustatory flushing, there was a decrease of the erythema after botulinum toxin injection, although the difference was not significant.

Representative data obtained by using the ISPH technique for an individual patient are shown before (Fig 1) and after (Fig 2) botulinum toxin injection. The results for the sweat surface and sweat quantity are shown in Fig 3. The quantity of sweat as measured with the BP technique was significantly decreased after botulinum toxin injection ($P < 0.05$). In addition, the surface of sweating as measured by the ISPH method was significantly decreased by the botulinum toxin infiltration ($P < 0.001$)

DISCUSSION

About 40% of patients undergoing parotidectomy will be disturbed by the symptoms of Frey syndrome.[1,11] So far, the available treatments have either been of temporary benefit or are associated with potential side effects that are more important than the symptoms to be treated. The treatment of Frey syndrome with botulinum toxin injection, following a suggestion of Drobik and Laskawi,[24] appears an attractive option.

Table 1. Characteristics of the botulinum toxin type A dilution and doses in publication on Frey syndrome treatment with botulinum toxin

Study	Year	No. of patients	Botox dilution	Interinjection distance	Dose per injection (mL)	Dose per patient (U)	Maximal dose used
Bjerkhoel and Trobbe[35]	1997	14	25 U/mL	1 cm	0.1	38 ± 12	62.5
Naumann et al[38]	1997	45	20 U/mL	1.5 cm	0.05-0.1	21 ± 14	72
Laccourreye et al[23]	1998	12	25 U/mL	1 cm	0.1	65	88
Laskawi et al[37]	1998	19	25 U/mL	2 cm	0.1	31	100
Dulguerov	1998	16	50 U/mL	1 cm	0.1	41 ± 22	75

The action of botulinum toxins is that of highly specific endopeptidases that cleave 3 different proteins (synaptosome-associated protein, synaptobrevin, and syntaxin) involved in the fusion of exocytosis vesicles with the cell membrane.[30] The action of botulinum toxin type A is on synaptosome-associated protein.[31] Although this action could occur in any cell, the extremely high specificity for cholinergic synapses is due to specific membrane proteins found only in the presynaptic endings of cholinergic synapses.[32] After binding, the toxin is internalized by endocytosis and liberated in the presynaptic cytosol. By blocking the exocytosis mechanism of the presynaptic terminal, the release of acetylcholine is inhibited. The synapse remains intact but is nonfunctional, and for neuromuscular junctions, this results in muscle paralysis.[33] The recovery of neuromuscular function is due to collateral sprouting from the same or other axons and the formation of new synapses.[33]

Numerous advantages can be cited for the use of botulinum toxin for the treatment of Frey syndrome. The substance is relatively well known and has been used for a variety of pathologies in the last 20 years with few side effects.[34] Its use is rather simple in the office setting, avoiding complicated procedures in the operating room. The only disadvantages are the pain associated with the needle sticking and the associated reluctance of some patients to be stuck, especially on the face. The pain associated with the needle injection was evaluated by our patients to be minimal (2 of 10 on an analog visual pain scale), a result found also in other studies.[23,35] Whether the use of local anaesthetic cream (EMLA, Astra, Sweden) will increase patient's acceptance of this mode of treatment[35] remains to be seen.

There were no facial paralysis side effects of the botulinum toxin injection, as reported by others.[23,35] It is difficult to understand how a strictly intradermal injection can result in the paralysis of facial nerve branches. Also, the membrane receptors responsible for the cholinergic specificity of botulinum toxins are located only in the presynaptic terminals and not in nerve fiber trunks. Therefore the most plausible explanation of these rare and partial temporary paresis is an injection deep to the dermis and diffusion to facial motor end plates.

Before a widespread acceptance of this mode of treatment, the technical aspects in terms of botulinum toxin dilution, interinjection distances, doses per injection site, and maximal doses per patient should be determined (Table 1).[23,35,37,38] There seems to be an agreement on the 10-mm interinjection distance and on an injection dose of 0.1 mL. The 10-mm interinjection distance is supported by the data of Shaari and Sanders[36] for neuromuscular junctions: injections 10 mm away from the motor end plate band of the rat tibialis anterior muscle are ineffective in inducing paralysis. In the same experimental system, increasing the dose and volume of botulinum toxin resulted in increased paralysis. A 20-fold increase in the dose doubled the paralysis; however, little gain was achieved with injection doses above 5 U.[36] As far as volume is concerned, a 100-fold increase in volume was necessary to double the paralysis.[36] Studies on human sweat glands partially support these data.[39]

Small volumes of concentrated botulinum toxin have the advantage of minimizing the diffusion and possible side effects. However, if side effects do occur, they would be more disabling because of the higher concentration.[36] We used a concentration of 50 U/mL, with the idea that a smaller volume of injection will produce less discomfort and be more efficacious. This is probably necessary in zones with intense facial gustatory sweating (dark zone in Fig 1, *A*). However, others[23,35] have obtained good results with a lower dilution (25 U/mL), and this dosage might be advantageous in patients who have a large surface of gustatory sweating.

The follow-up of our patient population is shorter than 1 year (median, 3 months), and therefore we can only speculate about the duration of the effect. In a recent publication, Laskawi et al[37] have found that the effect of botulinum toxin on gustatory sweating is rather long lasting, with an average delay to recurrence of 15 months.

We have the impression that the new methods that were developed for the evaluation of gustatory sweating (and especially the ISPH method)[28] are invaluable for deciding the zones to treat and the amount of botulinum toxin that should be injected. Although the Minor test provides indispensable topographic information, it is cumbersome to use[28] and poorly tolerated by patients,[40] and it provides neither a permanent record nor quantitative data.[28] Also, in areas of intense gustatory sweating, bluish discoloration tends to drip down the face, which results in a smear, rendering the collection of precise topographic information difficult. Possibly, with a more widespread use of the ISPH technique, the technical details of the botulinum toxin treatment for Frey syndrome can be further advanced.

CONCLUSION

1. The treatment of Frey syndrome by intradermal injection of botulinum toxin type A appears simple, effective, reliable, and fast and is devoid of major side effects.
2. Further work is required to determine the minimal dose per injection, the maximal interinjection distance, and the long-term duration of the effect.
3. The ISPH and the BP techniques are accurate, objective, and topographic methods to localize Frey syndrome and evaluate the response to treatment.

We thank Drs Marco Pelizzone (Cochlear Implants Center) and Denis Salomon (Clinic of Dermatology and Venerology) for their suggestions and ideas that led to the development of the ISPH and BP methods. Dr A. Arechalde's help for the collection of the skin temperature and color is also acknowledged.

REFERENCES

1. Laage-Hellman J-E. Gustatory sweating and flushing after conservative parotidectomy. Acta Otolaryngol (Stockh) 1957;48: 234-52.
2. Laage-Hellman J-E. Gustatory sweating and flushing. Aetiological implications of response of latent period and mode of development after parotidectomy. Acta Otolaryngol (Stockh) 1958;49:306-14.
3. Frey L. Le syndrome du nerf auriculo-temporal. Rev Neurol 1923;2:92-104.
4. Baillarger M. Mémoire sur l'oblitération du canal de Sténon. Gazette Médicale de Paris 1853;23:194-7.
5. Duphenix M. Observations sur les fistules du canal salivaire de Stenon. Sur une playe compliquée à la joue ou le canal salivaire fut déchiré. Mémoires Académie Royale de Chirurgie 1757;3: 431-9.
6. Dulguerov P, Marchal F, Gysin C. Frey syndrome before Frey—the correct history. Laryngoscope 1999;109:1471-3.
7. Thomas A. Le double réflexe vaso-dilatateur et sudoral de la face consécutif aux blessures de la loge parotidienne. Rev Neurol (Paris) 1927;1:447-60.
8. Ford FR, Woodhall B. Phenomena due to misdirection of regenerating fibers of cranial, spinal, and autonomic nerves: clinical observations. Arch Surg 1938;36:480-96.
9. Haxton HA. Gustatory sweating. Brain 1948;71:16-25.
10. List CF, Peet MM. Sweat secretion in man: IV. Sweat secretion of the face and its disturbance. Arch Neurol Psychiatr 1938;40: 443-70.
11. Dulguerov P, Quinodoz D, Cosendai G, et al. Prevention of Frey syndrome during parotidectomy. Arch Otolaryngol Head Neck Surg 1999;25:833-9.
12. Leriche R. Behandlung der permanenten parotis Fisteln durch die Entnervung der Speicheldrüse Ausreissen des N auriculotemporalis. Zentralbl Chir 1914;41:754-5.
13. Glaister DH, Hearnshaw JR, Heffron PF, et al. The mechanism of post-parotidectomy gustatory sweating (the auriculo-temporal syndrome). BMJ 1958;2:942-6.
14. Debets JMH, Munting JDK. Parotidectomy for parotid tumours: a 19-year experience from the Netherlands. Br J Surg 1992;79: 1159-61.
15. Gardner WJ, McCubbin JW. Auriculotemporal syndrome: gustatory sweating due to misdirection of regenerated nerve fibers. JAMA 1956;160:272-7.
16. Golding-Wood PH. Tympanic neurectomy. J Laryngol Otol 1962;76:683-93.
17. Hays LL. The Frey syndrome: a review and double blind evaluation of the topical use of a new anticholinergic agent. Laryngoscope 1978;88:1796-824.
18. Needles W. The auriculotemporal syndrome. With a suggestion regarding therapy. Arch Neurol Psychiatr 1936;35:357-60.
19. Laage-Hellman J-E. Treatment of gustatory sweating and flushing. Acta Otolaryngol (Stockh) 1958;49:132-43.
20. May JS, McGuirt WF. Frey's syndrome: treatment with topical glycopyrrolate. Head Neck 1989;11:85-9.
21. Laccourreye O, Bonan B, Brasnu D, et al. Treatment of Frey's syndrome with topical 2% diphenanil methylsulfate (Prantal): a double-blind evaluation of 15 patients. Laryngoscope 1990;100: 651-3.
22. Sessions RB, Roark DT, Alford BR. Frey's syndrome—a technical remedy. Ann Otol 1976;85:734-9.
23. Laccourreye O, Muscatelo L, Nuade C, et al. Botulinum toxin type A for Frey syndrome: a preliminary prospective study. Ann Otol Rhinol Laryngol 1998;107:52-5.
24. Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. Acta Otolaryngol (Stockh) 1995;115:459-61.
25. Schulze-Bonhage A, Schroder M, Ferbert A. Botulinum toxin in the therapy of gustatory sweating. J Neurol 1996;243:143-6.
26. Dale HH, Feldberg W. The chemical transmission of secretory impulses to the sweat glands of the cat. J Physiol 1934;82:121-8.
27. Fox RH, Goldsmith R, Kidd DJ. Cutaneous vasomotor control in the human head, neck, and upper chest. J Physiol 1962;161:298-312.
28. Dulguerov P, Quinodoz D, Vaezi A, et al. New objective and quantitative tests for gustatory facial sweating. Acta Otolaryngol (Stockh) 1999;119:599-603.
29. Minor V. Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung. Dtsch Z Nervenheilkd 1927;101:302-8.
30. Montecucco C, Schiavo G, Tugnoli V, et al. Botulinum neurotoxins: mechanism of action and therapeutic applications. Mol Med Today 1996;2:418-24.
31. Blasi J, Chapman ER, Link E, et al. Botulinum type A selectively cleaves the synaptic protein SNAP-25. Nature 1993;365:160-3.
32. Coffield JA, Considine RV, Simpson LL. The site and mechanism of action of botulinum neurotoxin. In: Jankovic J, Hallett M, eds. Therapy with botulinum toxin. New York: Marcel Dekker Inc; 1994. p. 3-13.
33. Borodic GE, Ferrante RJ, Pearce LB, et al. Pharmacology and histology of the therapeutic application of botulinum toxin. In: Jankovic J, Hallett M, eds. Therapy with botulinum toxin. New York: Marcel Dekker Inc; 1994. p. 119-57.

34. Jankovic J, Hallet M. Therapy with botulinum toxin. New York: Marcel Dekker Inc; 1994.
35. Bjerkhoel A, Trobbe O. Frey's syndrome: treatment with botulinum toxin. J Laryngol Otol 1997;111:839-44.
36. Shaari CM, Sanders I. Assessment of the biological activity of botulinum toxin. In: Jankovic J, Hallett M, eds. Therapy with botulinum toxin. New York: Marcel Drekker Inc; 1994. p. 159-70.
37. Laskawi R, Drobik C, Schöebeck C. Up-to-date report of Botulinum toxin type A treatment in patients with gustatory sweating (Frey's syndrome). Laryngoscope 1998;108:381-4.
38. Naumann M, Zellner M, Toyka KV, et al. Treatment of gustatory sweating with botulinum toxin. Ann Neurol 1997;42:973-5.
39. Bushara KO, Park DM, Jones JC, et al. Botulinum toxin—a possible new treatment for axillary hyperhydrosis. Clin Exp Dermatol 1996;21:276-8.
40. Belly E, Valentini V, Matteini C. Ruolo dello SMAS nella prevenzione della sindrome di Frey. Minerva Stomatol 1996;45:569-74.