# Hyperhidrosis: Evolving Therapies for a Well-Established Phenomenon

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**The socially embarrassing disorder of excessive sweating, or hyperhidrosis, and its treatment options are gaining widespread attention. In order of frequency, palmar-plantar, palmar-axillary, isolated axillary, and craniofacial hyperhidrosis are distinct disorders of sudomotor regulation. A common link among these disorders is an excessive, nonthermoregulatory sweat response often to emotional stimuli in body regions influenced by the anterior cingulate cortex as opposed to the thermoregulatory sweat response regulated by the preoptic-anterior hypothalamus. Diagnosis of these mechanistically ambiguous disorders is primarily from patient history and physical examination, whereas results of laboratory studies performed with indicator powder reveal the distribution and severity of resting hyperhidrosis and document the integrity of thermoregulatory sweating. Treatment options lie on a continuum based on the severity of hyperhidrosis and the risks and benefits of therapy. In general, therapy begins with antiperspirants or anticholinergics. Iontophoresis is available for palmar-plantar and axillary hyperhidrosis. Botulinum toxin type A or local excision / curettage is effective for isolated axillary hyperhidrosis not responsive to topical application of aluminum chloride. Endoscopic thoracic sympathectomy may be used for severe cases of palmar-plantar and palmar-axillary hyperhidrosis. No sole therapy of choice has emerged for craniofacial sweating. The long-term sequelae of hyperhidrosis and its treatment also are discussed.**

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**BT-A = botulinum toxin type A; CH = compensatory hyperhidrosis; ETS = endoscopic thoracic sympathectomy; TST = thermoregulatory sweat test**

Excessive sweating, or hyperhidrosis, is a socially embarrassing disorder that may seem trivial to the general public because of its falsely perceived rarity; however, hyperhidrosis is being recognized increasingly, and its treatment options are gaining widespread attention.[1-3] Both ancient and modern medicine have been perplexed by this entity. Of sweating, Hippocrates used the term *hidroa*, which was translated from Greek into Latin and English as *sudamina*. Both terms gave rise to the present use of *hidrosis* and *sudomotor function*.[4] Nearly 100 years ago, Meachen[5] described hyperhidrosis and 3 therapeutic goals that have withstood time: "…1) To seek out the underlying cause for the increased sweating and endeavor to remove it; 2) to check or modify the amount of secretion itself; and 3) to relieve any secondary dermatitis or other complications that may arise."

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A question-and-answer section appears at the end of this article.

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## DEFINITIONS

The condition that results when the sudomotor system (which controls sweat output) functions excessively in isolation with no apparent cause is termed *primary* or *essential hyperhidrosis*. It is imperative to differentiate this condition from *secondary hyperhidrosis*, which can be associated categorically with infection, malignancy, neurologic and endocrine disorders, spinal cord injury, and miscellaneous causes (Table 1).[6] An important contemporary cause, terrorism-related chemical warfare agents (such as organophosphate compounds that inhibit acetylcholinesterase, similar to agricultural pesticides), must be included in this list.[7]

Primary hyperhidrosis is classified as focal or generalized on the basis of the stimulus and site of neuromodulation. The exaggerated sweating response to emotional or sensory stimuli probably originates in the anterior cingulate frontal cortex as opposed to thermoregulatory sweating, which is primarily regulated by the preoptic-anterior hypothalamus.[8] Focal hyperhidrosis most commonly affects the palms (Figure 1, top) and soles. Excess sweating in these areas is called palmar-plantar hyperhidrosis. Isolated axillary hyperhidrosis affects only the underarms and may coexist with palmar-plantar hyperhidrosis. Finally, and least common, there is isolated supranormal sweating of the face (craniofacial hyperhidrosis), which may be provoked by heat, emotion, or spicy foods (gustatory hyperhidrosis). This disorder is difficult for patients to hide, especially if the facial skin forms a darkened hue called chromhidrosis.

## EPIDEMIOLOGY

A recent survey in the United States suggests that the prevalence of primary (essential) hyperhidrosis is 2.8%, with approximately one half (1.4%) of these individuals projected to have axillary hyperhidrosis and one sixth (0.5%) projected to have sweating that is intolerable or interferes with daily activities.[9] Epidemiological data spe-

TABLE 1. **Categories of Secondary Hyperhidrosis**

| Category | Pathogenesis | Features |
|---|---|---|
| Chronic infection | Tuberculosis, brucellosis | Night sweats |
| Neuroendocrine malignancy | Pheochromocytoma | Paroxysmal sweating, sudomotor cholinergic activation from excess catecholamines; responds to anticholinergics |
| Endocrinologic | Thyrotoxicosis, diabetes mellitus | Paroxysmal sweating, increased metabolism and increased sensitivity of nerve fibers to epinephrine; thyrotoxicosis responds to β-blockade |
| Malignancy | Leukemia, lymphoma, renal cell carcinoma, Castleman disease | Night sweats, pruritus; may respond to plasmapheresis or histamine$_2$ receptor antagonists |
| Neurologic diseases | Acromegaly, carcinoid syndrome, diencephalic epilepsy, basilar artery occlusion–pontine ischemia | Paroxysmal sweating; pontine ischemia may damage decending inhibitory fibers |
| Biochemical agents | Acetylcholinesterase inhibitors, chemical warfare, pesticides | Responsive to removal of stimulus, anticholinergics |
| Spinal cord injury | Autonomic dysreflexia, orthostatic hypotension, posttraumatic syringomyelia | Can occur months to years after injury to spinal cord |
| Miscellaneous | Anxiety, hypoglycemia, menopause | |

cific to palmar hyperhidrosis are sparse, but this condition affects an estimated 0.6% to 1.0% of the Western population.[10] The prevalence of severe palmar hyperhidrosis varies geographically and has been described as endemic in Southeast Asia, where it affects up to 3% of the population.[10,11] This high prevalence in Southeast Asia can be seen in the staggering group sizes (1167-9988 patients) in several outcome studies of thoracoscopic sympathectomy.[12-14] On review of these and other large-scale reports,[12-17] several conclusions can be drawn. Of patients with severe hyperhidrosis presenting for surgery, most have palmar-plantar hyperhidrosis, 15% to 20% have combined palmar-axillary hyperhidrosis, 5% to 10% have isolated axillary hyperhidrosis, and less than 5% have craniofacial hyperhidrosis. Hyperhidrosis is heritable in autosomal dominant fashion with variable penetrance; a recent study on allelic probability estimates that a child of a parent with palmar hyperhidrosis has a likelihood of phenotypic expression of 0.28, meaning the child has an approximate 25% chance of developing hyperhidrosis.[18] Most large studies report that 25% to 50% of patients with palmar hyperhidrosis have a family history of the disorder. No other risk factors are known to cause primary hyperhidrosis.

## MECHANISMS

Understanding why patients have supranormal sweating of the hands and feet begins with understanding the complex interaction between thermoregulatory sweating and emotional sweating. Thermoregulatory sweating is the major mechanism of heat dissipation by whole-body eccrine glands, is controlled by the preoptic area of the hypothalamus, and is diurnal or nocturnal. Emotional sweating, always diurnal, is controlled by the anterior cingulate cortex, and its distribution is limited usually to the face, axillas, palms, and soles.[8] Both higher centers descend to synapse on the intermediolateral cell column neurons of the spinal cord. From there, myelinated preganglionic sympathetic nerves exit the cord via the ventral roots and enter the segmental paravertebral sympathetic ganglia or course up and down the sympathetic chain and enter paraverterbral ganglia at other levels. Unmyelinated postganglionic sympathetic fibers exit the ganglion and rejoin the segmental spinal nerve or plexus, eventually innervating pilomotor (hair follicles), sudomotor (sweat glands), and vascular effectors of the skeletal muscle and skin of the trunk and limbs.

Sudomotor nerves release acetylcholine onto the muscarinic cholinergic receptors of the sweat glands (Figure 2). There are 2 million to 5 million sweat glands in the body, and they are anatomically and functionally differentiated into eccrine and apocrine. Developed in utero, eccrine sweat glands are ubiquitous in skin but are heavily concentrated in the forehead, scalp, axillas, palms, and soles.[19] Glabrous or hairless skin (palms, soles, lips) is rich in arteriovenous anastomoses (bypass conduits between arterioles and venules) that are richly innervated by sympathetic vasoconstrictor nerves.[20] Thus, in addition to emotional sweating, glabrous skin is a source of thermoregulation and heat release. In the dermis, eccrine gland secretory coils secrete an isotonic, slightly acidic solution (with sodium, potassium, and chloride ions) into the sweat ducts, which reabsorb sodium chloride and produce hypotonic sweat destined for the epidermis. The apocrine glands are small and inactive until puberty, when they become larger and produce a secretion thicker than sweat. Localized to the

axilla, areola of the nipple, and perineum in humans, apocrine gland secretion is of little physiological importance; in other mammals, it may function as a sexual attractant.

In nonhyperhidrotic individuals at normal body temperature in a comfortable environment, the low level of sweat production in the eccrine glands of the palms and soles is controlled by the neocortical emotional component. As the temperature increases, hypothalamic thermoregulatory control of nonglabrous skin is activated primarily with minor effects on palmar and plantar sweating. If mental stress is added to the setting of heat stress, palmar and plantar sweating increases further.[21] In palmar hyperhidrosis, a hyperfunctioning, emotional component of the central sudomotor nervous system occurs, evidenced by the observation that excess sweating does not occur during sleep and is aggravated by emotional stimuli. During mental stress, increased skin sympathetic nerve activity and pronounced vasoconstriction,[22] excessive sweating,[23] and an associated increase in evaporation[24] collectively cause cold, "clammy" hands. There is pronounced vasoconstriction of the hand with a markedly low cutaneous temperature at rest, which is exaggerated during cooling maneuvers.[25-27] Furthermore, sweating is excessive during exercise[25] and whole-body heating, suggesting a hyperfunctioning hypothalamic thermoregulatory component that compounds the emotional component of sweating.[28] Finally, regional anesthesia injections on the ulnar nerve of a patient with palmar hyperhidrosis produce warm, dry skin in dermatomal fashion.[23] Together, these findings suggest that primary hyperhidrosis (1) is most likely caused by hyperfunctioning central sudomotor output, (2) has a predominantly emotional component, (3) is associated with a more tonically active sympathetic innervation of vasomotor downstream effectors and a more labile innervation of sudomotor effectors, and (4) can be ameliorated by sympathetic denervation.

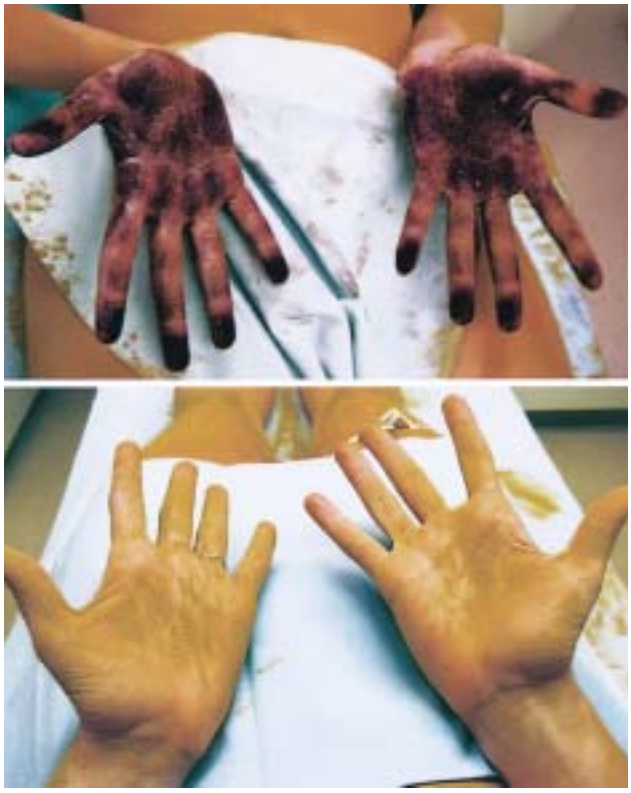

FIGURE 1. A young, healthy patient with primary palmar-plantar hyperhidrosis in resting conditions at room temperature. Top, A mixture of starch, alizarin red, and sodium carbonate is placed on the palms of a hyperhidrotic patient at rest whose core temperature is then elevated, changing the indicator color from light orange to purple. Bottom, Test is repeated in the same patient under the same conditions 2 months after successful endoscopic thoracic sympathotomy (see text).

## DIAGNOSIS

### Patient History and Examination

A substantial part of the diagnosis of hyperhidrosis can be achieved by obtaining a patient history. Patients describe excessive sweating that began in childhood or adolescence. Palmar hyperhidrosis interferes with nearly all tasks of manual dexterity. Avoidance of handshake can lead to professional embarrassment, and avoidance of touch can lead to social or interpersonal seclusion. These symptoms put patients at risk for higher levels of disability, fear, avoidance, and other physiological symptoms (blushing, trembling) that may encompass social anxiety disorder.[29] Palmar hyperhidrosis usually is accompanied by plantar hyperhidrosis, which is easier to conceal but when extreme may cause bromhidrosis (foul-smelling sweat), infection, and skin maceration. Isolated axillary hyperhidrosis is more indicative of abnormal apocrine and eccrine sweating under both thermoregulatory and emotional control. Patients with this disorder change clothing repeatedly and usually have already explored numerous over-the-counter antiperspirants. Gustatory hyperhidrosis can be a normal response to certain foods, whereas the rare primary craniofacial hyperhidrosis is provoked by emotional and environmental stimuli similar to palmar-plantar hyperhidrosis.

### Clinical Laboratory Testing

Once secondary causes of hyperhidrosis have been ruled out, dermatologic and/or autonomic laboratories have several techniques to stratify the severity of sweating. The Minor starch-iodine test delineates the area of sweating using iodine solution, 3.5% in alcohol, applied to clean, dry shaved skin.[30] Dry starch powder is applied lightly; sweat causes the mixture to turn dark blue, highlighting the loca-

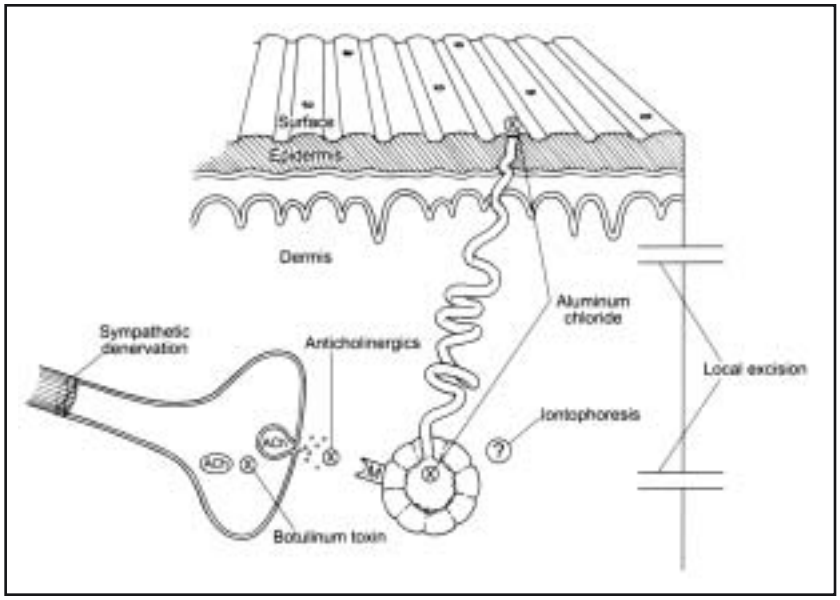


FIGURE 2. A sympathetic sudomotor nerve and an eccrine sweat gland in glabrous skin. Included are the mechanisms of action of the therapeutic modalities for hyperhidrosis (see text). Surgical sympathetic denervation actually is performed more proximally, under video-assisted thoracoscopy, interrupting the corresponding extremity innervation along the thoracic sympathetic chain. The mechanism of action for iontophoresis is unknown. ACh = acetylcholine; M = muscarinic cholinergic receptor.

tion of sweating. A waterproof marker can be used to outline the area, then simple gravimetric analysis is performed on the sweat. This consists of weighing filter paper on a high-precision scale, placing it over the defined region for 60 seconds, then reweighing; thus, the rate of sweat production is defined as milligrams per minute per centimeters squared.[2,31] Dynamic sudorometry using a ventilated capsule method also has been used to quantify sweat output and response to treatment of hyperhidrosis.[32,33]

We use the thermoregulatory sweat test (TST) at our institution both to delineate the distribution of primary hyperhidrosis and to reveal the integrity of skin thermoregulatory sweating in response to a controlled heat and humidity stimulus.[28] The TST at the Mayo Clinic is a modification of the Guttman quinizarin sweat test.[34] Low et al[35] revived the TST by introducing alizarin red indicator to replace quinizarin, the latter often irritating and sensitizing the skin. Fealey et al[28,36] modified Guttman's cabinet so that ambient humidity was regulated and infrared heaters controlled skin temperature. The TST begins with a whole-body skin application of a mixture of alizarin red, cornstarch, and sodium carbonate.[37] The entire anterior body surface and palmar and plantar skin are powdered. Resting (essential) hyperhidrotic areas become evident almost instantly and are photographed (Figure 1). The patient is then placed in a tented heating cabinet where skin and oral temperatures and thermoregulatory sweat recruitment patterns are recorded. Oral (core) temperature is elevated to 38.0°C, at which point all healthy patients sweat profusely, turning the light orange–alizarin red mixture dark purple. The patient is removed from the cabinet and photographed again, and a computer drawing is obtained. The percentages of anhidrosis and hyperhidrosis areas are computer determined from measurements of the different colored regions of body surface area. The distribution of both resting hyperhidrosis and thermoregulatory sweating is obtained, providing an important adjunct in making the diagnosis. Patients with hyperhidrosis typically continue to sweat profusely from the palms and soles while heated, differing from nonhyperhidrotic subjects. Usually all other surface areas sweat normally with a rare patient exhibiting anhidrosis elsewhere. The TST can help confirm and stratify the success and durability of subsequent therapy.

## TREATMENT

### Anticholinergics and Clonidine

Perhaps unknowingly, early practitioners contributed to the understanding of the mechanism of sweat production by finding that giving elixirs from atropine plants improved this condition.[38] For palmar-plantar hyperhidrosis, systemic anticholinergics such as atropine and glycopyrrolate are seldom used because of adverse effects (eg, sedation, dry mouth, constipation) and the emergence of newer ther-

TABLE 2. **Medications for Hyperhidrosis**

| Type of hyperhidrosis | Treatment | Formulation | Route of administration and dosage |
|---|---|---|---|
| Craniofacial, gustatory | Glycopyrrolate | 0.5% Solution, cream, or roll-on | Topical, daily; tapered when able |
| | Clonidine | 0.1-mg tablet | Oral, incremental increases up to 0.6-1.2 mg/d in 2 or 3 divided doses |
| | | Transdermal patches, 0.1-0.3 mg/d | 0.1 mg/d patch first week; increase weekly up to two 0.3 mg/d patches |
| Craniofacial, gustatory, menopausal | Bellergal-S | 0.3-0.6 mg of ergotamine tartrate, 0.2 mg of belladonna alkaloids, and 40 mg of phenobarbital | One tablet by mouth every 12 h. May need to be compounded by local pharmacy because it is less available than in the past |
| Axillary, palmar-plantar, craniofacial | Aluminum chloride | 20% Aluminum chloride in ethyl alcohol; 12% aluminum chloride in sodium carbonate–water | Topical, nightly, until desired effect is achieved, then taper to once per week; follow *Physicians' Desk Reference* directions carefully for best results |
| Palmar-plantar, axillary | Iontophoresis unit | Patient-controlled current, 15-30 mA using tap water (from faucet); if this is not effective, glycopyrrolate, 2-mg tablet, can be crushed and added to each water tray | Topical, at each site for 30 min once or twice daily, or 20 min at each site every 2-3 days, or 10 min at each site 3-5 times weekly; the anode site is most effective so switch sides after half of each treatment |

apies. However, for craniofacial hyperhidrosis, medications are currently the most effective therapy (Table 2). Daily application of a topical 0.5% glycopyrrolate solution has been reported to improve craniofacial sweating.[39] The sympathetic inhibitory action of the $\alpha_2$-adrenergic agonist clonidine has been reported in a patient for whom the dose was increased by increments of 0.05 mg/d until reaching a dose of 0.3 mg/d to 0.4 mg/d, with most of the dose (0.25 mg) taken at bedtime to avoid daytime sedation. As an adjunct, nightly application of 20% aluminum chloride in ethyl alcohol (discussed subsequently) was tapered eventually to every fifth night. By week 3, the patient experienced complete remission with the additional purported benefits of anxiolysis.[40]

### Antiperspirants

Over-the-counter antiperspirants contain metal salts, most commonly aluminum chloride, which purportedly blocks the epidermal sweat duct or promotes atrophy and vacuolization of the glandular secretory cells.[41] For more severe cases in which excessive sweat reacts with aluminum chloride to form irritating hydrochloric acid, anhydrous ethyl alcohol added to 20% aluminum chloride hexahydrate is prescribed.[42] The solution must be applied to dry skin, typically before sleep, and washed off 6 to 8 hours later. Effectiveness may be improved by covering the treated area with a T-shirt for axillary application, a shower cap for scalp application, or plastic wrap and overlying gloves or socks for palmar or plantar application, respectively. This should be performed nightly until a desired response is achieved, and frequency of application should be titrated to once or twice per week. Disadvantages include only temporary relief lasting a few days, ineffective relief in severe cases, and cumbersome application. Many patients may have tried this treatment for the hands but may not have followed all the steps just described. In that case, another trial is given with strict adherence to details of the technique, which are clearly described in the *Physicians' Desk Reference* summary page for the drug. This is still the treatment of choice for axillary hyperhidrosis.

### Iontophoresis

Since 1984, commercial iontophoresis devices have been available for home use. The mechanism of action is unknown. The battery-powered unit delivers a current through tap water–saturated wool pads, separated by a nonconducting barrier placed directly on the treatment site. Patients increase amperage to the maximum output tolerable and treat each site for 30 minutes, up to twice daily.[43] Patients may require daily treatments for up to 2 weeks, which should decrease sweating for several weeks, and repeat treatments as needed.[43] Adverse effects may include pain and small skin burns from the direct current; therefore, alternating current applicators are being developed.[44] Recently, Dolianitis et al[45] have shown iontophoresis with a 0.05% glycopyrrolate solution to be significantly superior to tap water in suppression of palmar hyperhidrosis. Further development and standardization of the technique and equipment for iontophoresis should substantially enhance this treatment alternative.

### Botulinum Toxin

Previously used as an off-label treatment for hyperhidrosis, the US Food and Drug Administration approved the use of botulinum toxin type A (BT-A) for axillary hyperhidrosis in July 2004. Odorless, tasteless, and colorless, botulinum is the most poisonous substance known.[46] Botulinum toxin type A is 1 of 7 types (A-G) of botulinic toxins from the

gram-positive bacillus *Clostridium botulinum*. It was isolated in 1946 in crystalline form and 4 years later was discovered to paralyze a hyperactive muscle on injection.[47] At the sympathetic nerve bouton innervating an eccrine sweat gland, the heavy chain of the BT-A molecule is internalized by receptor-specific endocytosis, and the light chain interferes with a synaptosomal protein, thereby blocking exocytotic release of acetylcholine.[47,48] The longer-lasting inhibition of sweating appears related to BT-A's induced functional denervation of sweat glands, on the basis of immunofluorescence results obtained from growth-associated protein (GAP) 43/protein gene product (PGP) 9.5 stained skin biopsies from patients with palmar hyperhidrosis.[49] Patients can develop antibody titers against BT-A, but this is extremely uncommon with the limited dosing used for palmar or axillary hyperhidrosis.

Botulinum toxin type A is injected intradermally in the affected areas. To reduce the pain of injections, several analgesic therapies have been described, including oral or intravenous sedation medication, topical lidocaine cream, nerve blocks, intravenous regional anesthesia (Bier block), and recently, cryoanalgesia with dichlorotetrafluoroethane.[50] For axillary hyperhidrosis, the BT-A dose is typically 50 to 100 U per axilla, diluted in preserved 0.9% saline. Approximately 20 injections are distributed evenly in the hyperhidrotic area outlined by the Minor starch-iodine test. Sweat reduction should be noticeable in 2 to 4 days and should be substantial within 2 weeks after the first injection.[31,51] Average therapeutic duration is approximately 7 months because sweat function returns gradually over time; subsequent injections are necessary approximately every 4 to 17 months.[51,52]

Disadvantages of BT-A for palmar hyperhidrosis include repeated, uncomfortable injections into the hand that necessitate some form of analgesia or sedation as well as the potential spread of botulinum into the neuromuscular junctions of surrounding muscle beds causing weakness of the thumb–index finger pinch.[53] The risk of intrinsic hand muscle weakness can be minimized by intradermal injection and small-volume reconstitution of BT-A. Nevertheless, a preliminary short-term study has shown that the Dermatology Life Quality Index is significantly improved by BT-A injection in patients with hyperhidrosis of the axillas, palms, or both.[54]

### Local Excision

Only applicable for axillary hyperhidrosis, newer techniques of localized surgical removal of eccrine and apocrine sweat glands have gained in popularity since the unsightly or restrictive en bloc excisions were first performed in the 1960s. Both axillary liposuction and curettage, aimed at removing the sweat glands in the dermis-subcutaneous fat junction, can be performed under local anesthesia with use of small incisions, with or without systemic administration of anxiolytics. In general, patients first undergo starch-iodine delineation of the axillary sweat region. After injection of local anesthesia with a vasoconstrictor, a small incision is made, followed by sharp superficial curettage or liposuction. A suction drain may be placed with skin sutures, or the incision may be left open to drain and heal spontaneously, depending on the procedure and the preference of the proceduralist. Significant postoperative improvements in sweating and satisfaction lasting from 6 weeks to 6 months are reported in approximately 80% to 90% of patients.[55-57] Efficacy should be permanent. Disadvantages to the procedure include a potential for scarring, partial alopecia, or hyperpigmentation.[56] Self-limited, short-term adverse effects may include bruising, induration, and pain.[56] Increased operator experience and evolving techniques have substantially improved the appeal of this procedure for axillary hyperhidrosis.

### Sympathetic Denervation

After anticholinergics and topical antiperspirants, thoracic chain sympathectomy is the next oldest of the current therapies for palmar hyperhidrosis.[58] Thoracic chain sympathectomy remains successful for long-term therapy for severe palmar hyperhidrosis and, interestingly, for plantar hyperhidrosis, which improves modestly in about 50% to 75% of the patients and in perhaps 80% of patients with coexisting axillary hyperhidrosis.[37] For isolated axillary hyperhidrosis and craniofacial hyperhidrosis, variant techniques are used.

Historically, surgical sympathectomy was reserved for severe cases of palmar hyperhidrosis refractory to the more conservative therapies for several reasons: the invasive nature of the procedure, the need for general endotracheal anesthesia and hospitalization, and perioperative and postoperative complications. Several surgical approaches have been described, evolving to the present minimally invasive video-assisted endoscopic thoracic sympathectomy (ETS), for which 1 small intercostal incision is used for uniportal access in each lateral axilla.

Outcome studies after ETS have received criticism because many end points are subjective and potentially conflict with objective studies. Despite patient satisfaction, TST and starch-iodine test results may reveal partial sweating, sympathetic skin response studies may normalize, and vasomotor studies of cooling and rewarming kinetics also may normalize.[27,37,59,60] For consistency, the term "operative success" typically signifies objective proof of denervation and diminished sweating. In experienced hands, this is greater than 90% and correlates clinically with long-term measurable anhydrosis. The phrase "considered the operation successful" pertains to the patient's subjective satis-

faction in the reduction of original focal sweating. This usually follows objective criteria and is expressed typically in more than 95% of patients but may not correlate with the postoperative degree and area of anhydrosis included in the "operative success" criteria of the postoperative sweat test measurement discussed previously. In fact, dry palms are a satisfying result of modern surgery regardless of how the surgery is performed. "Pleased with overall outcome" combines overall satisfaction with any accompanying adverse effects such as compensatory hyperhidrosis (CH), which typically lower the "overall satisfaction" to approximately 85%.[15,17,37,61-65]

Perioperative complications include the following: life-threatening great vessel injury (extremely rare); hemopneumothorax requiring chest tube placement (1%); and prolonged transient or intercostal neuralgia (1%-2%), which can be minimized with smaller endoscopes and a unipolar approach (J.L.D.A., unpublished data, February 2005). However, unless catastrophic or unusually complicated, perioperative complications typically have a low bearing on the overall patient satisfaction rate. In contrast, cosmetic complications from ETS include Horner syndrome (ipsilateral ptosis, miosis, facial anhydrosis, vasomotor rhinitis) and, most importantly from a patient-satisfaction perspective, an increase in sweating elsewhere on the body (CH). To minimize these complications, much attention has been focused on how, and how much, sympathetic nerve innervation should be interrupted.

Once it was determined that the second thoracic sympathetic ganglion was the largest physiological relay center to the upper extremity,[66] surgical therapy for hyperhidrosis has included vigilant avoidance of damage to the stellate ganglia (Figure 3). Before the 1940s, Horner syndrome resulted from surgery because the stellate ganglion was removed.[58] With endoscopic visibility, the 5% complication rate for Horner syndrome from older supraclavicular or posterior thoracic surgical approaches has been lowered to 1% to 2%.[15,17,37,61-65] Only in severe cases of craniofacial hyperhidrosis is stellate ganglionectomy considered, and this occurs after the patient has undergone a preoperative stellate nerve block to accept the cosmetic sequelae of Horner syndrome. The variant operation for isolated axillary hyperhidrosis generally involves sympathetic chain ablation inclusive of more sympathetic chain segments, starting at T2 or T3, and ablation of each segment caudally to approximately T4.[62]

Compensatory hyperhidrosis is by far the most common and disagreeable complication of sympathectomy, producing subjective and objectively measurable increased sweating in body segments usually just below the areas made dry by sympathectomy. With traditional sympathectomies or ganglionectomies (Figure 3), severe CH may occur in 10% to 40% of postoperative patients.[37] It is interesting that the sites affected with CH are generally the thermoregulatory, nonglabrous skin regions of the trunk/back, buttocks, groin, and thighs that sweat normally before ETS. A plausible explanation is that CH results from more aggressive procedures targeting resection of several ganglia, intervening chain, or white rami communicantes and their axons from cells in the intermediolateral cell column of the spinal cord. Henceforth, large areas of anhidrosis occur with increased severity of CH, such that normal thermoregulatory effectors become up-regulated as a mechanism of normal heat dissipation.[67] This may lead ultimately to long-term debilitating CH with few treatment options, and at least 5% of patients may regret undergoing the operation.[65]

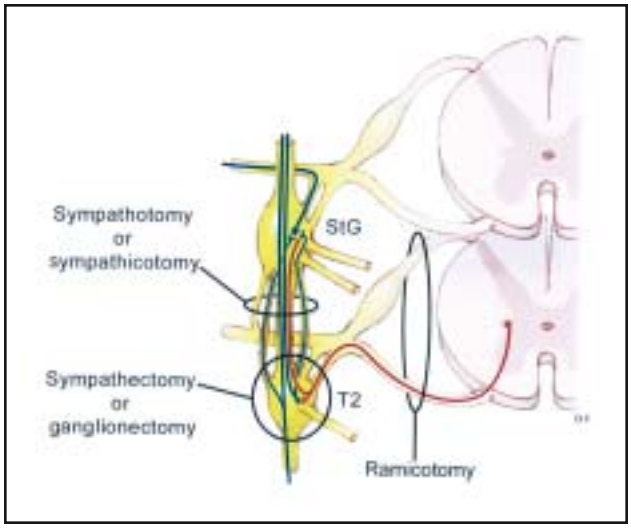


FIGURE 3. The sympathetic chain and the various targets of surgical sympathetic denervation. Preganglionic sympathetic nerves (including sudomotor nerves) exit the spinal cord from segments T1 to L2-3 and course up and down the paravertebral sympathetic chain to innervate postganglionic nerves. Often, the inferior cervical ganglion is fused with the first thoracic ganglion, called the stellate ganglion (StG), which must be spared to minimize the risk of postoperative Horner syndrome (see text). Ganglion-sparing endoscopic thoracic sympathotomy is restricted to electrocauterization of the chain between the stellate and T2 ganglion, minimizing the risk of severe postoperative compensatory hyperhidrosis in other regions of the body.

Typical surgical sympathectomies for palmar hyperhidrosis have consisted of excision or electrocautery ablation of the T2 and/or T3 sympathetic ganglion. Recently, our institution modified this technique by preserving the ganglia and performing a simple chain disconnection between the T2 ganglion and the stellate ganglion (Figure 3). Termed *sympathotomy*, this procedure produces excellent results and clinically diminishes the chances of severe CH.[37] Termed *sympathicotomy* in other countries, this technique and the disconnection of sympathetic rami (*rami-*

*cotomy*) will require further long-term investigation of the postoperative risk of severe CH.

Intraoperative predictability of successful outcome depends on monitoring of the acute response to surgical denervation and abrupt release of sympathetic tone. These modalities include assessment of instantaneous skin blood flow changes with laser-Doppler flowmetry and increases in fingertip or palmar skin temperature. Importantly, the average intraoperative fingertip temperature increase of 1.2°C with sympathotomy in our experience is lower than the skin temperature increase of about 3°C reported with more destructive procedures.[68] This has important implications in the choice of intraoperative monitoring techniques because smaller changes in temperature, when considered alone, may raise doubt about the procedure's therapeutic efficacy. Therefore, we routinely monitor skin blood flow with laser-Doppler for real-time surgical feedback, serving as an adjunct to fingertip temperature, which lags by 3 to 5 minutes.[68]

Information on the long-term physiological sequelae is emerging rapidly. Preoperatively, in addition to abnormal sudomotor control, sympathetic cardiovascular regulation may be affected mildly in severe cases of hyperhidrosis. A blunted reflex bradycardia response to parasympathomimetic maneuvers such as Valsalva maneuver or cold water face immersion, as well as an increased heart rate response to orthostatic stress, suggests a hyperfunctioning sympathetic discharge that is reversed after ETS.[25,69] Because sympathetic cardiac accelerator fibers exit the spinal cord from segments T1 to T4, ETS is believed to simulate a mild physiological β-adrenergic blockade.[70] This is because the heart rate at rest and during maximal exercise is lower 6 weeks postoperatively,[69,71] but exercise capacity is not affected. As for pulmonary sympathetic denervation, no significant detrimental effect on pulmonary function has been shown in children and adults.[72] The return of vasomotor function[27,73] has rendered ETS less desirable for conditions such as Raynaud phenomenon and chronic regional pain syndrome.

### Cost

The costs of surgical treatment of hyperhidrosis considerably exceed those of nonsurgical treatment. These initial differences may be attenuated with time, if the need for long-term treatment in nonsurgical patients is factored in. Cost differences also may be related to the success of treatment in individual patients, the experience of the health care clinicians, the regional differences in overall health care costs, and the methods of reimbursement. Potential differences in costs with these evolving treatments can be estimated most accurately if the sponsoring physician first assesses the extent of the patient's disease and the individual patient or physician questions the clinicians most likely to care for the patient.

## SUMMARY

One of the oldest described dermatologic conditions, primary hyperhidrosis is an embarrassing disorder that, even today, is misconceived as rare and untreatable. It is exacerbated during emotional stress, and the pathophysiological mechanism appears to be hyperfunctioning efferent sudomotor outflow, controlled by the anterior cingulate cortex. Primary hyperhidrosis is associated with few or minimal autonomic comorbidities. Treatments are based on the severity of sweating intertwined with the risks and benefits of each modality. Increased medicosocial awareness and evolving therapies are improving the efficacy of treatment and minimizing adverse effects. For more information, patients can be referred to the International Hyperhidrosis Society (www.sweathelp.org), a nonprofit global organization that provides education, advocacy, access to hyperhidrosis treatment, and research into excessive sweating.

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## Questions About Hyperhidrosis

1. Which *one* of the following statements about hyperhidrosis is *false*?
   a. It can be a heritable disorder in 25% to 50% of cases
   b. It affects adolescents of any ethnic background
   c. It is bothersome during sleep
   d. The pathophysiological mechanism is unclear
   e. The prevalence approaches 2.8% of the US population

2. Which *one* of the following statements about the diagnosis of primary hyperhidrosis is *false*?
   a. The history and physical examination have more bearing than laboratory studies in making the diagnosis
   b. Numerous autonomic abnormalities coexist with hyperhidrosis
   c. Long-term exposure to pesticides or biochemical agents may mimic primary hyperhidrosis
   d. Patients will describe symptom exacerbation during stressful situations
   e. It must be differentiated from secondary hyperhidrosis

3. Which *one* of the following would *not* present similar to hyperhidrosis?
   a. Thyrotoxicosis
   b. Chronic lymphocytic leukemia
   c. Tuberculosis
   d. Menopause
   e. Pure autonomic failure

4. Which *one* of the following treatments is extremely *effective* against axillary hyperhidrosis and recently received Food and Drug Administration approval?
   a. BT-A injections
   b. Oral glycopyrrolate
   c. Local surgical curettage
   d. Surgical sympathectomy
   e. Aluminum chloride salts

5. Which *one* of the following surgical objectives attempts to minimize severe postoperative CH?
   a. Stellate ganglion excision
   b. Minimally invasive sympathetic chain disruption
   c. Sympathetic chain disconnection at several levels
   d. Open thoracotomy procedure with multiple ganglion excisions
   e. No method of minimizing this complication exists

Correct answers:
1. *c*, 2. *b*, 3. *e*, 4. *a*, 5. *b*