Hyperhidrosis: definition and different forms

Sweating is an important mechanism in the regulation of body temperature. Hyperhidrosis is defined as the production of excess sweat, beyond the amount required to return elevated body temperature to normal, which is slightly below 37°C.

Hyperhidrosis can be divided into primary and secondary forms. Primary, or essential, hyperhidrosis occurs typically in young individuals experiencing mental stress (nervous sweating), without other pathogenetic factors. The sweating is focal and located chiefly in the axillae, the palms of the hands, the soles of the feet, or the forehead. Secondary hyperhidrosis is caused by an underlying neurologic or endocrinologic disease or malignancy. The sweating is usually diffuse (Table 10.1).

Primary or focal hyperhidrosis is caused by the overactivity of normal sweat glands and not by glandular hypertrophy. Focal hyperhidrosis is diagnosed in individuals if the area of excess sweating is visibly focal and excessive for at least 6 months without any apparent cause and is associated with at least two of the following characteristics:

- Bilateral and relatively symmetric sweating
- Impairs daily activities
- Frequency of at least one episode per week
- Age of onset less than 25 years
- Positive family history
- Cessation of focal sweating during sleep.

Histopathologic samples from patients with primary hyperhidrosis do not show an increase in the number or size of sweat glands. Sweating episodes are mediated by escalating sympathetic activity, channeled through sudomotor fibers that innervate the eccrine sweat glands. Patients suffering from focal hyperhidrosis who are exposed to mental stress can demonstrate a greater than 10-fold increase in activity of the sudomotor fibers, compared to non-hyperhidrotic controls exposed to the same level of stress, because the severity of hyperhidrosis is very individualized.

There is a genetic predisposition and a family history of focal hyperhidrosis in 30–65 per cent of patients suffering from the disorder. About 1–2 per cent of the population suffers from hyperhidrosis. In the United States alone, 2.8 per cent of the population, or 8 million...
individuals, is affected with hyperhidrosis. The estimated number of unknown cases may be even higher for several reasons:

- Patients are not aware that hyperhidrosis is a disease and have learned to live with their symptoms.
- Patients do not know whom they should approach for advice (family practitioner, dermatologist, neurologist, endocrinologist)
• Patients may be told to live with their hyperhidrosis, because of their physician’s lack of knowledge of treatment options.

The subjective grading of the severity of sweating is wide: some patients are hardly disturbed by excessive sweating, whereas others ask for treatment for negligible sweating. Essential hyperhidrosis is the most common skin disease associated with co-morbidity of psychiatric disorders (anxiety, neurosis, depression). The psychopathologic characteristics of patients with essential hyperhidrosis can be divided into three groups:

• Patients with objective hyperhidrosis associated with a psychosomatic disorder.
• Patients with objective hyperhidrosis associated with a secondary psychiatric reaction arising from the chronic skin disease (sociophobia, depression, anxiety).
• Patients with body dysmorphic disorder (BDD – a disturbed body image resulting in a pathologic concern about appearance and an extreme lack of self-confidence and self-identity), without any objective symptoms of essential hyperhidrosis.

While treatment of hyperhidrosis in the first two groups can ameliorate the psychologic distress, patients with BDD must be protected from invasive treatment and should be referred for psychiatric assessment (see prologue).

Anatomy of sweat glands

Sweat glands are found all over the body. Their total number is between 2 and 4 million. There are two types of sweat glands: eccrine sweat glands, forming the majority (Table 10.2), and apocrine sweat glands, which are present only in limited areas such as the axillae, perianal region, areolae, periumbilical region, prepuce, scrotum, mons pubis, and labia majora. The ratio between apocrine and eccrine sweat glands is 1:1 in the axillae, but 1:10 in other regions.

<table>
<thead>
<tr>
<th>Area</th>
<th>Quantity (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sole of foot</td>
<td>620</td>
</tr>
<tr>
<td>Forehead</td>
<td>360</td>
</tr>
<tr>
<td>Palms</td>
<td>300</td>
</tr>
<tr>
<td>Axillae</td>
<td>300</td>
</tr>
<tr>
<td>Thigh</td>
<td>120</td>
</tr>
<tr>
<td>Scrotum</td>
<td>80</td>
</tr>
<tr>
<td>Back</td>
<td>65</td>
</tr>
<tr>
<td>Lips</td>
<td>None</td>
</tr>
<tr>
<td>Nail bed</td>
<td>None</td>
</tr>
<tr>
<td>Nipple</td>
<td>None</td>
</tr>
<tr>
<td>Inner preputial surface</td>
<td>None</td>
</tr>
<tr>
<td>Labia majora</td>
<td>None</td>
</tr>
<tr>
<td>Glans penis</td>
<td>None</td>
</tr>
<tr>
<td>Glans clitoridis</td>
<td>None</td>
</tr>
</tbody>
</table>
Eccrine sweat glands

Eccrine sweat glands are long-branched, tubular structures with a coiled secretory portion and a straight ductal portion. The secretory coil is situated deep in the dermis; clear and dark cells can be distinguished within its epithelium. Clear cells have a round, large, moderately euchromatic nucleus. The major constituents of sweat – water and electrolytes – are formed by the clear cells. Dark cells have a cuboidal shape and secrete PAS-positive glycoproteins from dense granules within their cytoplasm. These glycoproteins are the most prominent protein constituents of sweat. The function of dark cells is unknown.

Eccrine sweat glands are innervated by sympathetic nerve fibers from the spinal cord. Nerve cells from spinal cord segments T1 to T4 supply the skin of the face (thoracic segment of the spinal cord), from T2 to T8 the skin of the upper limbs; from T4 to T12 the trunk, and from T10 to L2 the lower limbs (lumbar segment of the spinal cord). An understanding of this innervation is important for the surgical treatment of hyperhidrosis with endoscopic thoracic sympathectomy (see below).

Apocrine sweat glands

Apocrine sweat glands consist of a basal secretory coil and a straight duct leading to the skin surface. The secretory region is situated in the deep dermis. The secretory cells are cuboidal, but may be squamous when the gland is distended with secretory product. The ducts of apocrine glands are morphologically similar to the eccrine ducts. The innervation of apocrine glands is similar to that of the eccrine glands - by sympathetic nerve fibers coming from the same spinal segments as those of the eccrine glands. The secretory product of apocrine glands is a sterile, thick, milky, and odorless fluid containing protein, carbohydrate, ammonia, lipids, ferric ions, and fatty acids. The characteristic smell is generated only after bacterial decomposition. Apocrine sweat glands may be a relic of human evolution: in animals, the secretory product contains pheromones that are an important signal for potency and territorial behavior. However, their particular teleonomic function in humans is still not clear.

Pathophysiology of sweating

Thermoregulation

Sweating is one of the physiologic bodily functions that helps provide for constant body temperature. The normal perspiration rate is approximately 0.5–1 ml/min, i.e. 1–2 liters per day. However, in stressful situations up to 10 liters per day can be produced. Other thermoregulatory mechanisms include changing the diameter of peripheral blood vessels and modifying metabolic and muscular activity. Increasing peripheral cutaneous blood circulation achieves heat loss by convection (i.e. heat emanating from a radiator); sweating, on the other hand, generates evaporative heat loss from the body surface. As with all vital homeostatic regulatory systems of the body, sweating is controlled by the autonomic nervous system, located in the hypothalamus. The body is very sensitive to increases in temperature, which should be always slightly below 37°C (98.7°F). An increase of only 0.5°C (to 99.5°F) causes discomfort; an increase of 1°C (to 100.4°F) causes collapse. Several factors modify thermoregulation in the hypothalamic center, including hormones, pyrogens, physical activity, and emotional stimuli. Temperature changes during the menstrual cycle and thermoregulatory imbalances during the climacteric are not well understood. Emotional and physical activity also can influence the thermoregulatory center via the limbic system.
Mechanism of sweat secretion

The secretory activity of the human eccrine sweat gland consists of two major functions: secretion of an ultrafiltrate of a plasma-like precursor fluid by the secretory coil in response to acetylcholine released from the sympathetic nerve endings, and re-absorption of sodium in excess of water by the duct, producing hypertonic sweat on the skin surface.

Sato originated the concept of an ionic mechanism of fluid secretion by the clear cells of the eccrine acini of exocrine glands. Acetylcholine, released from periglandular cholinergic nerve endings in response to nerve impulses, binds to cholinergic receptors in the clear cells of sweat glands. The activation of these receptors stimulates an influx of extracellular calcium into the cytoplasm (Figure 10.1) that stimulates chloride channels in the luminal membrane and potassium channels in the basolateral membrane, causing a net KCl efflux from the cell. The cell volume therefore decreases, because water follows the solutes to maintain iso-osmolarity, and the cell shrinks. The decrease in potassium and chloride concentration provides a favorable chemical potential gradient – probably the driving force for Na–K–2Cl co-transporters located in...
the basolateral membrane. The co-transporters carry sodium, potassium, and chloride ions into the cell in an electrically neutral fashion. In the steady state of secretion, potassium and sodium ions recycle across the basolateral membrane without further loss. In contrast, chloride ions enter the cell via the Na–K–2Cl co-transporters. The movement of chloride ions across the apical (luminal) membrane causes depolarization and generates a negative luminal potential. This then attracts sodium ions into the lumen across the Na-conductive intercellular junction. Thus, the sodium and chloride ions that enter the lumen form NaCl in the isotonic primary fluid.

In the coiled portion of the sweat duct, re-absorption of NaCl occurs to preserve electrolytes, creating the hypotonic sweat secreted at the skin surface. The absorption of NaCl by the duct is due to the active transport of sodium ions by the Na pump located in the basal ductal cell membrane (Figure 10.2). Chloride ions are also transported against the chemical gradient, but down a favorable electrical gradient. In cystic fibrosis, Cl channels in the luminal membrane are defective and those in the basal membrane are significantly decreased, resulting in excess chloride ions in the sweat secreted at the skin surface.

Topical treatments for focal hyperhidrosis

Antiperspirants

Only about 5 per cent of the approximately 3 million sweat glands distributed all over the body are active at any given time during rest or normal activity. This leaves 95 per cent of the 3 million sweat glands ready to become activated during stressful and abnormal situations. Body odors can be unpleasant to many observers; consequently much effort is put into stifling and removing them, chiefly by the use of antiperspirants or deodorants. Whereas deodorants act with fragrance and antibiotics, antiperspirants reduce the flow of sweat. In most deodorants, the active antibacterial agent is triclocarbon or triclosan. Antiperspirants have some degree of antibacterial activity, owing to their acidity.

Over the years, many theories have been suggested for the mechanism of action of antiperspirants. In 1967, Papa and Kligman summarized the efforts of more than 20 years of research with the words: ‘Next to nothing is known concerning the way in which aluminium salts inhibit eccrine sweating’. Sulzberger’s theory that a periductal infiltrate of lymphocytes causes hypohidrosis has been abandoned, as has the suggestion of an increase in permeability of aluminium salts in the acrosyringium, leading to complete dermal re-absorption of the sweat. In 1981 Quatrale et al. used fluorescence microscopy to demonstrate the presence of a plug of electron-dense, amorphous material in the stratum corneum (Figure 10.3). Hölzle confirmed this by finding PAS-positive material in the upper part of the stratum corneum in the dilated
lumen of secretory glands, with atrophy of the secretory cells. He concluded that sweat glands show a tendency to atrophy after long-term use of antiperspirants.

The most widely used ingredients for topical antiperspirants are aluminum salts. Aluminum chloride hexahydrate (AlCl-H), introduced by Stillians in 1916, is one of the most effective metallic antiperspirants. Unfortunately, AlCl-H has a high incidence for causing either irritant or even contact dermatitis. Aluminum hydrochloride is therefore preferred because this is less toxic, causes less skin irritation and allergic dermatitis, and is less corrosive to different fabrics. However, it is less effective than AlCl-H, and so aluminum hydro chloride is used in a concentration of 30 per cent. Aluminum salts in concentrations less than 20 per cent usually are not effective and are therefore only used in cosmetic products. Contrary to the manufacturer's recommendation, the solution or cream should be used every night before sleeping, and not every second or third night. In addition, it is very important to use the cream or solution in sufficient quantities only before bedtime, because for crystallization of the stratum corneum plug to occur, complete anhidrosis of the affected areas is absolutely necessary. Preparations containing zirconium salts have been abandoned, mainly because of their role in producing rare cases of skin granulomas, probably due to a delayed-type allergic reaction.

Anticholinergic drugs (parasympatholytics)

Anticholinergic drugs (postsynaptic ganglia blockers) are mentioned here for completeness. Anticholinergic medications work through the inhibition of parasympathetic postsynaptic membrane receptors on sweat glands. The receptors consist of three muscarinic subtypes: M1,
M2, and M3. The M1 subtype is found on nerve cells and autonomic ganglia. M2 is found on heart, smooth, and skeletal muscle. The M3 subtype is found on smooth muscle, endocrine cells, and glands. While anticholinergics block all receptors non-specifically, the action at the M3 subtype reduces perspiration in patients with hyperhidrosis. Currently, hyperhidrosis approved medications include propantheline bromide (Pro-Bathine®), glycopyrrolate (Robinul®), oxybutynin (Ditropan®), and benztropine (Cogentin®) (Table 10.3). In addition, atropine is often used in a tap water mixture in iontophoresis, a therapy that uses electrical current applied to the skin to induce hypohidrosis. Glycopyrrolate is currently the only anticholinergic that can be found in a 1 per cent topical formulation. The other medications are systemic agents that must be taken orally.

Owing to their adverse effects profile, the use of anticholinergics is limited mostly to selected patients who manifest multifocal or generalized hyperhidrosis. These include patients with hyperhidrosis of different sites occurring in unison or separately such as the axillae, forehead, neck, and scalp. Systemic medication is best used in such cases because different sweating sites can be treated at the same time. Parasympatholytics are categorized as either tertiary (atropine, scopolamine) or quaternary nitrogen compounds (methylscopolamine, N-butylscopolamine, methanthelin). The major indication for these antimuscarinic drugs is generally Parkinsonisms. The resorption of tertiary compounds is very good, the quaternary less so, being only 10–25 per cent resorbed. The list of side effects of these drugs is extensive and relatively severe. One of the most prominent side effects is the inhibition of perspiration. Other side effects include mydriasis, dry mouth and eyes, gastrointestinal disturbance, dizziness, blurred vision, tachycardia, urinary retention, and constipation. Because of the danger of glaucoma, parasympatholytics should not be prescribed without a prior ophthalmologic consultation. The half-life of postsynaptic ganglia blockers is relatively short (a few hours). This requires the consumption of medication by mouth three or four times a day, which easily and quickly becomes a compliance issue. In addition, owing to dose-dependent side effects, the dosage of the drug has to be titrated by increasing its strength slowly, until the desired degree of hypohidrosis is reached, while sustaining a modicum amount of other side effects. The dosage can therefore differ between patients, and patients usually are encouraged to titrate their medication up to a dose they can best tolerate. Many times these medications are not well tolerated by patients and are commonly discontinued after a short course.

### TABLE 10.3 SYSTEMIC ANTICHOLINERGICS COMMONLY USED TO SUPPRESS HYPERHIDROSION

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopyrrolate 1% cream</td>
<td>Apply 1% solution to affected area once daily</td>
</tr>
<tr>
<td>Glycopyrrolate (1 mg tablet)</td>
<td>1–2 mg PO bid/tid, titrate to effect</td>
</tr>
<tr>
<td>Oxybutrin</td>
<td>5 mg PO bid/tid; not to exceed 5 mg qid</td>
</tr>
<tr>
<td>Propantheline bromide</td>
<td>15 mg PO bid/tid 30 min ac initially; gradually titrate to effect</td>
</tr>
<tr>
<td>Benztropine</td>
<td>1–2 mg/day PO; not to exceed 6 mg/day</td>
</tr>
</tbody>
</table>
Tap-water iontophoresis

The basis of iontophoresis was first described by Ichihashi in 1936, but therapeutic administration of electricity has been known for over two centuries. As early as 1740, Pivati used iontophoresis in the treatment of arthritis. The mechanism of iontophoresis is based on the principle of electricity: elements with the same charge repel each other, while oppositely charged ones attract. The penetration of charged molecules across the epidermis is therefore facilitated by the use of an external current. For many years, iontophoresis has been used to facilitate transport of molecules (mainly drugs), which otherwise would not penetrate the skin.

Levit was the first to introduce tap-water iontophoresis (TWI) into practical dermatotherapy. The mechanism of TWI-induced anhidrosis has been much studied, but remains unclear. The suggestion that an obstruction high in the sweat duct leads to anhidrosis has been rejected, because no structural changes in the eccrine sweat glands are seen on light and transmission electron microscopy and because the low current densities are well below the threshold of damage to the acrosyringium. Wang et al demonstrated that the composition of neurotransmitters, the density of skin innervation, and the distribution of skin innervation do not change after iontophoretic treatment. Sato et al confirmed that anodal current has more of an inhibitory effect than cathodal current and that water is superior to saline, but increased concentrations of electrolytes diminished the therapeutic effect. Sato also confirmed that the inhibitory effect is a function of the current used. He concluded that the strong acidity generated by the hydrolysis of water in the anodal bath, and the further accumulation of hydrogen ions in the sweat duct by the anodal current, may be responsible for the inhibition of sweating, due to an unknown lesion in the sweat gland duct and acrosyringium.

The widely used, direct current (DC) iontophoresis is increasingly being replaced by alternating current with direct current offset (AC/DC) iontophoresis. For DC TWI a current of 8–25 milliamps (mA) at a voltage of 20–40 V is used, whereas for AC/DC TWI the same efficacy is achieved with a lower current (8–12 mA) and a fixed voltage of 16 V. In this mode, side effects such as burning and stinging sensations during treatment, erythema along the water surface, and especially electric shocks caused by abrupt changes in voltage (e.g. at removal from the bath) are minimized.

To achieve optimal results, TWI should be performed daily in the initial phase for about 10–14 days or until anhidrosis is achieved. At every treatment session, one extremity is bathed for 10 minutes in the anodal bath (Figure 10.4). Then the opposite extremity is bathed in the anodal pan for another 10 minutes. When palmoplantar hyperhidrosis is treated, both hands can be placed in one pan and both feet can be placed in the other pan. The polarity should be changed halfway through each therapy and not, as is sometimes recommended, every second session. After complete normhidrosis is reached, maintenance therapy is necessary on a weekly or twice-weekly basis.

Although TWI is effective in most cases, there are non-responders. For others, treatment with TWI is successful, but the patient’s willingness to continue with maintenance therapy may vary. Regular treatment schedules (e.g. every Monday evening while watching the news on television) can help to improve patient compliance. Alternative therapies, such as botulinum toxin injections (see below), systemic anticholinergic drugs, or surgery should be provided as alternative modes of therapy for non-responders and for patients who are unable for various reasons to continue with therapeutic iontophoresis. There are a few contraindications for TWI,
which include patients with pacemakers and metal orthopedic implants, and those who are pregnant\textsuperscript{21}. These patients should be offered an alternative mode of therapy.

**Surgical treatments for focal hyperhidrosis**

**Axillary sweat gland excision**

Both eccrine and apocrine sweat glands are predominately located in the superficial subcutis and the dermal–subcutaneous interface; indeed, some eccrine glands are located entirely in the dermis. It is important to appreciate this anatomy, since abrasive surgery such as curettage will not completely remove the dermal sweat glands and is therefore not recommended\textsuperscript{22}. Excision of the axillary skin and subcutaneous tissue en bloc represents the only comprehensive solution for severe cases of axillary hyperhidrosis that do not respond to botulinum toxin (see below).

Liposuction has the advantage of not leaving unsightly scarring but is much less efficient than excision, owing to the fact that it is a ‘blind’ technique with uncertain removal of all sweat glands. Because of this, the recurrence rate after axillary liposuction for hyperhidrosis is high, especially when many of the sweat glands reside in the lower dermis. In such cases, temporary anhidrosis is probably the result of physical damage to the fine superficial nerve plexi produced during liposuction, rather than because of the removal of the sweat glands. After several months the nerve plexi recover and the hyperhidrosis recurs.
CHAPTER 10: BOTULINUM TOXIN IN THE MANAGEMENT OF FOCAL HYPERHIDROSIS

Endoscopic thoracic sympathectomy (ETS)

The aim of this treatment is to achieve anhidrosis by a surgical sympathectomy of the hyperhidrotic area. The indications should be evaluated very carefully, owing to the technical difficulties of the procedure, its invasive nature, and the high complication rate. Serious complications, such as Horner syndrome or pneumothorax, are relatively rare (0.1 per cent and 0.3 per cent, respectively); however, there are reports of intraoperative cardiac arrest during ETS for palmar hyperhidrosis. Compensatory sweating is the most common side effect, occurring in up to 84 per cent of all cases, most of which are mild and unpredictable. However, up to one-third of the patients suffer from moderate to severe sweating over their entire body, especially over the trunk and the proximal extremities (Figure 10.5). The risk of compensatory hyperhidrosis increases with the location and extent of the area treated. Consequently, the risk for compensatory hyperhidrosis is higher in those who undergo ETS for facial or axillary hyperhidrosis than for those who are operated for palmar hyperhidrosis. This is so because after ETS for facial and axillary hyperhidrosis, the entire area of the body above the upper trunk and shoulders becomes anhidrotic. In addition, for technical and other reasons, there is no standardized ETS procedure for plantar hyperhidrosis, which is performed by laparoscopy. Because of the potential for grave post-operative complications, ETS must be strictly reserved only for severe hyperhidrosis of the palms that does not respond to any other treatment.

Botulinum toxin for focal hyperhidrosis

The history of botulinum toxin: from poison to medicine

The first recorded case of food poisoning caused by the neurotoxin-producing bacterium Clostridium botulinum (botulism) is believed to have been in 1735. In 1817 Dr Justinus Christian Kerner (1786–1862) published a very precise description of the symptoms of patients suffering from botulism after eating uncooked, smoked sausages or ham. The prominent clinical features of botulism include widespread parasympathetic symptoms such as blurred vision, diplopia, and dilated pupils, dry mouth with dysphagia, asthenia, constipation, nausea, vomiting, and abdominal cramps, followed by increasing muscle weakness descending from head to feet, and culminating in respiratory failure. Because very little was known about infections at that time, Kerner believed a fatty acid to be responsible for the illness. Pierre Emile...
van Ermengem (1851–1932), Professor of Bacteriology in Ghent, Belgium, isolated the responsible bacterium and refuted the fatty acid theory of Kerner. Before the First World War, Tchitchikine discovered the neurotoxin of *C. botulinum*, and it was Dr Hermann Sommer who first succeeded in purifying the exotoxin in 1920.

During the Second World War, much research was done in the Unites States at Fort Detrick, Maryland, principally by Edward J. Schantz, who was searching for an antidote to counteract botulinum toxin, which was thought to be a potential biologic weapon ready to be used by several other countries. In 1949 Burgen showed that the block of acetylcholine release by botulinum toxin occurred in the presynaptic nerve endings and not, as previously believed, by postsynaptic blockage of receptors, like atropine. In the 1960s Alan Scott, an ophthalmologist, was searching for a non-surgical alternative for the treatment of strabismus. His idea to weaken the extraocular muscles with botulinum toxin brought him in contact with Ed Schantz. After several trials on monkeys, botulinum toxin, serotype A (BTX-A) was approved in 1989 by the Federal Drug Administration for the treatment of strabismus, blepharospasm, and hemifacial spasm. Other fields of medicine quickly became interested and BTX-A was used for a wide variety of indications, in particular for the treatment of hyperkinetic muscles. Bushara was the first to suggest a possible indication for BTX-A in the treatment of hyperhidrosis. Since 2002, BTX-A has been approved for the treatment of axillary hyperhidrosis in many countries and most recently, in 2004, BOTOX® was approved in the USA by the FDA for axillary hyperhidrosis. There is little doubt that approval for the treatment of palmpoplantar hyperhidrosis with BTX-A will soon follow.

**Commercially available botulinum toxins**

Botulinum toxin type A purified neurotoxin complex is presently available as BOTOX® (Allergan, Irvine, CA, USA) and as Dysport® (Ipsen Ltd, Wrexham, UK). Botulinum toxin type B neurotoxin complex is distributed as Myobloc® in the United States (or as Neurobloc® in Europe) and is manufactured by Elan Pharmaceuticals (San Francisco, CA, USA). BOTOX® is vacuum dried and Dysport® is lyophilized and both are distributed in the form of a dry, crystalline powder that must be reconstituted with 0.9 per cent physiological saline, whereas Myobloc®/Neurobloc® is distributed as an aqueous solution with a pH of 5.6. The biological activity for all three products is defined in mouse units (MU) or just units (U): one mouse unit is defined as the amount of neurotoxin that is lethal in 50 per cent of female, 18–22 g Swiss-Webster mice (i.e. lethal dose, LD₅₀) after an intraperitoneal injection (i.e mouse LD₅₀ equals 1 mouse unit or U). It is very important to note that the equivalent units for the three products ARE NOT THE SAME, because the bacterial strain and the manufacturing process used to produce each individual product are entirely different from each other. The dose conversion factor between BTX-A (BOTOX®) and BTX-B (Myobloc®/Neurobloc®) according to the literature is 1:20; and between BOTOX® and Dysport® it is 1:4 (see Chapters 8 and 9). However, this should not be construed as a confirmatory statement of a ratio, since this ‘conversion’ is in direct conflict with the labelling of these products. The package inserts of both BOTOX® and Myobloc®/Neurobloc® reads: ‘Units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method’.

Before a physician uses any brand or serotype of botulinum toxin for a particular indication, it is wise for him or her to be familiar with the manufacturer’s literature and specifications for its use. However, as a general principle, the potency of one 500 U vial of BOTOX® is roughly equal
to the potency of one vial of Dysport®. Remember that any statement of a ratio of ‘conversion’ is in direct conflict with the labelling of these products, as stated above. There are currently studies underway in Europe and in the USA attempting to best define the conversion ratio between BOTOX® and Dysport® (see Chapter 8).

Birklein et al showed that BTX-B suppresses sudomotor function, effectively in a concentration-dependent manner. They carried out sweat tests (the quantitative sudomotor axon reflex test (QSART) and the minor iodine starch test, see below) before treatment and at 3 weeks, 3 months, and 6 months. They showed that a threshold dose of 8 U BTX-B leads to anhidrotic skin spots (>4 cm²) after 3 weeks and that the duration of anhidrosis was prolonged for 3 months with 15 U and for 6 months with 125 U of BTX-B. After 3 weeks, the QSART score had decreased to zero with doses of 62.5 U and more, and returned to 91 per cent of baseline after 3 months. After 6 months, recovery of sudomotor function was complete. A similar study was performed by the same group using BTX-A (Dysport®) that showed doses of 2.5 U/cm² of Dysport® or more lead to clinically relevant hypohidrosis. A resulting decrease in sweating was maintained for at least 6 months if 12.5 U/cm² were injected. Complete suppression could be achieved with doses of 20 U/cm² and above.

The onset of improvement of hyperhidrosis is believed to be earlier with BTX-B than with BTX-A and the overall effect and duration of both products are comparable to that of BTX-A, but they both are strongly dose-dependent. To ensure delivery of the labeled volume of drug, commercially available vials of botulinum toxin type B (M. myobloc®) are overfilled; the vial labeled as containing 2500 units of botulinum toxin type B in 0.5 ml actually contains approximately 4100 units in 0.82 ml; the vial labeled as containing 5000 units of botulinum toxin type B in 1 ml actually contains approximately 6800 units in 1.36 ml; and the vial labeled as containing 10,000 units of botulinum toxin type B in 2 ml actually contains approximately 12,650 units in 2.53 ml. Therefore, drug solution should not be diluted in the vial since this may result in a solution with a higher concentration of M. myobloc® than expected due to overfill.

Discomfort with injections of BTX-B is much higher, owing to its lower pH. This disadvantage can be reduced by using preserved saline instead of preservative-free saline when further diluting BTX-B. Dilution of BTX-B is done only at the discretion of the physician, since a vial of M. myobloc®/Neurobloc® comes already in solution. Furthermore, autonomic side effects occur far more often after indications of BTX-B than after BTX-A. Systemic symptoms such as dry mouth, heartburn, and constipation suggest a systemic spread of BTX-B. M. myobloc®/Neurobloc® may be useful in patients not responding to BTX-A, because of innate or acquired immunogenicity issues. However, to date there has been no report of secondary failure in patients treated with BTX-A for focal hyperhidrosis. Therefore current thought is that, due to the potential side effect profile of BTX-B, M. myobloc®/Neurobloc® should not be used as the first-line treatment of focal hyperhidrosis.

Patient management and practical considerations

Before treating patients with BOTOX®, a detailed patient history should be obtained, focusing particularly on clues for the presence of secondary hyperhidrosis, since the underlying primary disease must be addressed first. As with every other treatment, the potential side effects of the therapy, contraindications (Table 10.4), and the alternative treatments should be explained to the patient. It is also recommended that the patient understands the mechanism of action of BOTOX®, in particular, the need for re-injection after 6–9 months. All the different therapeutic
modalities (topical concentrated aluminum salt preparations, excision of the sweat glands, anticholinergic medications, or ETS) available should be explained to the patient. The example of a desk lamp can illustrate in simple terms the different therapeutic modalities available to treat hyperhidrosis. There are several different ways to prevent a lamp from casting light: either you take out the light bulb (sweat gland excision), or you cut through the electrical supply cord (ETS), or you temporarily insulate the light bulb contacts (BOTOX® injections).

It is very important that the patient understands the basic pharmacology of BOTOX® and possible side effects. The discussions should include the typical chronologic course required for

### TABLE 10.4 BOTOX® TREATMENT FOR HYPERHIDROSIS: CONTRAINDICATIONS AND POSSIBLE SIDE EFFECTS

**Contraindications**
- Secondary hyperhidrosis due to underlying disease
- Neuronal disease (e.g. myasthenia gravis)
- Pregnancy/lactation
- Intake of aminoglycoside antibiotics
- Severe coagulopathies

**Possible side effects**
- Stinging and burning during injection
- Small hematomas at injection sites
- Infection at injection sites
- Weakening of underlying muscles (except when treating the axillae)

I have been thoroughly informed about the above therapy by the doctor managing my treatment. I understand that the activity of my sweat glands will be decreased after the injection of purified botulinum toxin A (BOTOX®) into my skin. This effect will appear 3–7 days after the injections and last usually about 6 months, but its effect can last for a shorter or longer amount of time.

Additionally, I have received a leaflet about BOTOX® therapy that contains information that is complete and comprehensive, including alternative treatments. All my questions have been answered either by the treating physician or the nurse. I know that, owing to lack of evidence, BOTOX® should not be used in pregnancy or lactation. I am not aware that I am pregnant or have any significant neurological disease or systemic or local infection.

I understand that since 2003 BOTOX® has been approved by the FDA for the treatment of axillary hyperhidrosis only, but not for the treatment of palmoplantar or facial hyperhidrosis.

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<table>
<thead>
<tr>
<th>Date</th>
<th>Physician signature</th>
<th>Patient signature</th>
</tr>
</thead>
</table>
the clinical effects to become fully activated and the reasons and time for re-treatment. Patients should know not to be treated during pregnancy and lactation.

Many practitioners have the patient sign a written consent form that becomes part of the patient’s permanent record (see example in Table 10.5). Good follow-up procedures and prompt response to any complaints after treatment are important. The potential risks in treating patients for focal hyperhidrosis with BOTOX® are comparatively small. However, clearly the treating physician must know the pharmacologic effect of the drug and the anatomic sites to inject. It is necessary to participate in one or two training workshops to learn the injection technique prior to initiating treatment. Every practitioner must know in advance how to manage patients with unsatisfactory results. Successful treatments are predicated upon choosing the right patient for treatment, injecting them with the proper technique and insisting on adequate follow-up visits in order to administer appropriate follow-up care.

Axillary hyperhidrosis

Axillary sweating is not a life-threatening disease, but nonetheless can have a substantial impact on the quality of the sufferer’s life, both professionally and socially. Most patients with axillary hyperhidrosis have consulted many physicians in the past, most of the time without finding any substantial, long-lasting solution to their problem. In an open-label prospective study, we asked 251 patients about the impact of their focal hyperhidrosis on their lives (oral presentation at EADV, 2004, submitted): 68.5 per cent had to see more than two physicians (21.7 per cent more than three) before a correct diagnosis was made; 78.9 per cent suffered in their social and professional life due to their hyperhidrosis, 75 per cent were limited in their daily activity, and 50 per cent had to abstain from leisure activities. Naumann et al found similar data with 80 per cent of patients with at least a moderate limitation in daily activities and 72 per cent felt less confident or depressed (49 per cent). In fact, the negative impact of hyperhidrosis on a patient’s quality of life is comparable to conditions such as severe atopic dermatitis, cystic acne, or mild to moderate psoriasis. Focal hyperhidrosis should therefore be viewed as a substantive illness and not simply regarded as a lifestyle disorder.

Hyperhidrosis is a chronic condition requiring a safe, long-lasting treatment. It is advisable that treatment should be approached in a stepwise manner. In patients who do not respond to topical treatments – such as aluminum salt solutions or (for palmeroplantar hyperhidrosis) tap-water iontophoresis – intradermal injections of BOTOX® can solve the problem in only a few minutes and on an outpatient basis. In contrast to invasive surgical procedures such as excision, curettage, liposuction, or endoscopic thoracic sympathectomy, injections of BOTOX® can be performed without any anesthesia, are easy and quick to administer, and give highly effective results without any scarring. Most importantly, the administration of BOTOX® is associated with high patient satisfaction and low morbidity.

Minor starch test

It is essential to assess axillary hyperhidrosis objectively before treatment. A patient’s past medical history may not necessarily provide for a complete and accurate assessment of the severity of their hyperhidrosis. As mentioned above, an individual’s subjective assessment of suffering can be over- or underexaggerated. It is the task of the treating physician to separate patients with moderate hyperhidrosis - manageable with aluminum salt solutions - from patients with severe hyperhidrosis - to be treated with BOTOX®. Each patient should undergo
Figure 10.6 Performance of the Minor starch test. The hyperhidrotic area is doused with iodine solution (a) and after drying covered with starch powder (b). The hyperhidrotic area becomes clearly demarcated as a purple surface. Then the hyperhidrotic area is outlined (c). After removing the excess purple color from the center of the outline each injection site can be marked with gentian violet (d) to achieve the best results; (e) shows how the injections are placed.
CHAPTER 10: BOTULINUM TOXIN IN THE MANAGEMENT OF FOCAL HYPERHIDROSIS

the Minor starch test before treatment with BOTOX® (Figure 10.6). First the hyperhidrotic area is completely dried and covered with an iodine solution (i.e. Lugol or Betadine solution) (Figure 10.6a) and then sprinkled with powdered starch (e.g. cornflower starch) (Figure 10.6b). It is important that as little powder as possible is used to achieve a good colorimetric response. If too much powder is used, the powder will absorb the moisture of the sweat and the intensity of the patient's sweating may not be assessed correctly.

A semiquantitative measurement of focal hyperhidrosis can be achieved using the Minor starch test, demonstrating the full extent of sweating in the affected area and, through the intensity of the purple coloration, the severity of sweating. Therefore, by performing a Minor starch test before each treatment, the treating physician can determine how many injection sites and how much BOTOX® is needed prior to commencing therapy. It is advisable always to measure the affected area and document the colorimetric response with photographs and retain them as part of the patient's permanent record. This will allow comparison of efficacy before and after treatment during follow-up visits, and will allay any misgivings or feelings of dissatisfaction that the patient may fallaciously come to have.

Low-dose BOTOX® therapy, dilution, and injection technique

After outlining the affected area with a marker (Figure 10.6d), the axilla should be cleansed of all iodine and starch, and a final wipe down with denatured 70 per cent isopropyl alcohol should be performed before initiating the BOTOX® injections. Generally, a total dose of 50 U of BOTOX® (250 U of Dysport®) per axilla is required to adequately treat a moderately severely hyperhydrotic axilla. Therefore, no more than a total dose of 1 vial (100 U) of BOTOX® (500 U of Dysport®) should be used per patient, which is currently being recommended in the literature. This is based on the manufacturer's guidelines that recommend a vial of BOTOX® be reconstituted with preservative-free isotonic saline. Consequently, once the vial of BOTOX® is reconstituted without a preservative, it should be fully used within 4 hours, owing to the possibility the solution may not remain sterile for an extended period of time. However, no studies to date have been performed to verify the sterility of a reconstituted vial of BOTOX® after more than 4 hours. The package insert however still advises the administration of BOTOX® within four hours after the vial is removed from the refrigerator and reconstituted. During these four hours, reconstituted BOTOX® should be stored in a refrigerator (2° to 8°C). Every treating physician therefore has become accustomed to using one whole vial of BOTOX® per patient for obvious economic reasons. Over the years, however, we have learned that there are no adverse events or significant loss of potency resulting from the storage of reconstituted BOTOX® for a few days and even a few weeks.

There is BOTOX® stability data before reconstitution, for 5 days up to 30°C with insignificant effect on potency. Additionally, a freeze/thaw cycle that might have occurred does not affect product potency (personal communication, Roger Aoki, PhD). Consequently, physicians should abandon this practice and use the exact amount of BOTOX® each patient needs, predicated upon the size and severity of the affected area as defined by the Minor starch test.

The number of injection sites, and consequently the total dose of injected BOTOX®, should no longer be defined as a total recommended dose for a given anatomic site (i.e. 50 U of BOTOX® per axilla), but by the number of units used per injection site (i.e. 2 Units BOTOX® for each injection point). This also depends upon the size of the colorimetric response exhibited by
the Minor starch test, which in most patients is a surface area of approximately 8 × 4 cm to 10 × 5 cm (50 cm²). Since the diffusion capacity of BOTOX® is about 1.0 to 1.5 cm in diameter, 10 points injected at a distance of approximately 1.5 cm apart are sufficient to cover an area of 50 cm² (about a quarter of a vial of BOTOX® per side or half axilla per patient respectively). If this area is larger than 50 cm², we consequently need more injections (in general 15 to 20 points of injection i.e. three-quarters to one vial of BOTOX® per patient, meaning for treatment of both axilla). With this technique generally only half a vial of BOTOX® is used (Table 10.6), with no loss of efficacy. This technique is referred to as the ‘low dose, high volume botulinum toxin therapy’.

Higher doses (≥800 U) of BOTOX® have been used for therapeutic purposes, and they are associated with an increased risk of antigenicity and immunoresistance with the production of IgG-neutralizing antibodies.

The low-dose, high-volume technique has several advantages:

- Fewer injections
- Less painful treatment session
- Reduced incidence of neutralizing antibody production
- Reduced risk of immunoresistance
- Lower cost.

The optimal dilution of BOTOX® for the treatment of hyperhidrosis is still under discussion. Although the reconstitution of Dysport® with 5 ml of sterile saline is still widely accepted, Bigalke et al. showed that the biologic availability of Dysport® could be enhanced by:

- Lowering the concentration of the BTX-A (Dysport®)
- Supplementing reconstituted Dysport® with additional albumin
- Increasing the dilution volume.

Since this study was performed with Dysport®, which has a higher protein content than BOTOX®, its conclusions cannot and should not be extrapolated to the use of BOTOX®. The diffusion capacity of Dysport® was enhanced by increasing the volume of diluent used to

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**TABLE 10.6 SUGGESTED DILUTIONS AND UNITS USED TO TREAT AXILLARY HYPERHIDROSIS**

<table>
<thead>
<tr>
<th>Dilution</th>
<th>BOTOX® 10 ml</th>
<th>Dysport® 10 ml</th>
<th>BOTOX® 5 ml</th>
<th>Dysport® 5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>U/vial</td>
<td>100</td>
<td>500</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>U/ml</td>
<td>10</td>
<td>50</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>U/0.1ml</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>ml/injection site</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Number of injections/axilla</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>U/axilla</td>
<td>20</td>
<td>40</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Total U/patient</td>
<td>40</td>
<td>80</td>
<td>200</td>
<td>400</td>
</tr>
</tbody>
</table>
reconstitute the product. Specifically, instead of reconstituting a 500 U vial of Dysport® with 5 ml of normal saline (which provides 50 U of BTX-A for each 0.1 ml of solution), Bigalke et al. recommended reconstituting a 500 U vial of Dysport® with 10 ml of solute (which provides 5 U of BTX-A for each 0.1 ml of solution) (Table 10.6)³⁹.

Further, to avoid immunoresistance, the following recommendations should be considered:

• Use the smallest possible effective dose
• Extend the interval between treatments as much as possible
• Avoid booster injections.

Therefore this author prefers to reconstitute a 100 U vial of BOTOX® with 10 ml of normal saline, instead of 5 ml, and inject 2 U of BTX-A (10 U Dysport®) per 0.2 ml injection site (see Table 10.6).

Although there are as yet no published data on the development of resistance to BOTOX® therapy in patients with hyperhidrosis, we should be concerned about the potential for its occurrence. Therefore, the use of BOTOX® should be based on the required dose needed to treat each individual patient so that an appropriate clinical response can be obtained. There are also economic considerations: BOTOX® is expensive and, by reducing the required therapeutic dose, costs are kept down – both for the patient and the health care industry.

Hyperhidrosis of the palms and soles

The dilution of BTX-A (BOTOX® or Dysport®) for the treatment of hyperhidrosis of the palms or soles can be the same as that for the treatment of hyperhidrosis of the axilla (see above). However, to avoid attendant muscle weakness after BOTOX® injections, especially in the hands, the reconstitution volume for both BOTOX® and Dysport® can be reduced from 10 ml to 5 ml. Again, as the radial diffusion distance of BOTOX® is about 1.0–1.5 cm, the interval between two injection points should not exceed much beyond this diameter. Therefore, depending on the size of the hands or feet and the localization of the hyperhidrosis (sometimes not all the digits are involved), approximately 35–40 injection points should be planned for the treatment of one hand and 60–80 injection points for one foot, leading to a total dose of BOTOX® of approximately 80 U (320 U of Dysport®) per hand and 160 U (640 U of Dysport®) per foot.

In distinct contrast to the painless BOTOX® injections of the axillae for hyperhidrosis, BOTOX® injections of the palms and soles for hyperhidrosis require regional anesthesia.

Nerve block

Many trials of regional anesthesia have been reported, with differing results. Cooling sprays and topically applied EMLA® cream can provide limited skin surface anesthesia, but completely painless injections can only be achieved by nerve blocks, which commonly are poorly accepted by patients. The administration of nerve blocks requires careful and expert training. Nerve blocks can be painful and it is difficult to achieve a complete and total anesthesia in every patient. The risk of nerve injury and severe side effects (anaphylactic shock, cardiac problems) also should not be underestimated. Vasovagal syncopal episodes are common and the actual application of the procedure usually prolongs the overall time for the therapeutic procedure. Because of the effect of the anesthetic on motor muscle activity, patients are consistently inconvenienced (e.g. they are unable to drive or even shake hands for several hours or even days after a BOTOX® treatment.
session). To maintain the anhidrotic effect of BOTOX®, the injections, and thus the nerve block, have to be repeated on a regular base. Because of the many disadvantages of BOTOX® injections for nerve blocks in the palms and soles, particularly, the need for nerve blocks, many patients often postpone or even cancel the required second or subsequent treatment sessions, regardless of the excellent clinical outcomes they might have experienced previously.

A new anesthetic procedure for the treatment of palmoplantar hyperhidrosis therefore has been developed (see below). The use of nerve blocks then should be reserved for selected cases.

![Figure 10.7 The different injection points for a nerve block of the hand; the red squares indicate the points of injection. (a) for an ulnar nerve block: 1 = tendon of the flexor carpi ulnaris, 2 = tendon of the pulmaris longus; (b) for a median nerve block: 1 = tendon of the flexor carpi radialis; (c) where to block radial nerve (over the tendon of the extensor carpi radialis and medial of the radial artery)](image-url)
CHAPTER 10: BOTULINUM TOXIN IN THE MANAGEMENT OF FOCAL HYPERHIDROSIS

Hand block
To achieve complete anesthesia of the hand, all three nerves (ulnar, median, radial) have to be effectively blocked from transmitting a nervous impulse. To anesthetize the radial nerve, which lies in the superficial fascia at the wrist, 2–4 ml of 1–2 per cent lidocaine with or without epinephrine (1:100,000) is injected subcutaneously 1 cm parallel to the carpal bones on the dorsomedial aspect of the hand and over the tendon of the extensor carpi radialis and medial to the radial artery ventrally (Figure 10.7a–c). To anesthetize the median and ulnar nerves with or without epinephrine 1:100,000 but approximately 2 ml of lidocaine 1–2 per cent (reduce the burning pain of injection with 0.5 per cent sodium bicarbonate) can be injected on both sides of the tendon of the flexor carpi ulnaris (the ulnar flexor muscle of the wrist and ulnar nerve) and the tendon of the palmaris longus (the long flexor muscle of the palm and median nerve), respectively (Figure 10.7). The needle should be inserted 0.5–1 cm perpendicular to the skin until firm resistance is felt and the deep fascia is pierced. It is then retracted about 2 mm before the lidocaine is injected (alternatively, xylonest 1 per cent or carboestin 0.5 per cent may be used). After 15–30 minutes full anesthesia is achieved in the palm and the back of the hand. The totality of the block is discernible through loss of sensitivity, impairment of motor activity, and the hand becoming warm, red, and dry. This can be considered an advantage because the patient feels complete anhidrosis for the first time. However, because of the vasodilation, every injection site (30–40 per palm) tends to bleed copiously.

Foot block
The principle of a foot block is similar to the hand block (see above). The injection sites for the tibial nerve block are located on both sides of the tibial artery, dorsocaudal to the medial malleolus. The needle is inserted perpendicular to the skin and advanced 0.5–2 cm. Then 2 ml local anesthetic is injected (see above). For the saphenous nerve block, a subcutaneous infiltration of local anesthetic is made 2 cm above the ankles all around the lower leg. The fibularis profundus block is performed with an injection of 2 ml local anesthetic on both sides of the dorsal is pedis artery (Figure 10.8a–c). The foot block is relatively easy to perform, in many cases much easier than the hand block; however, the same disadvantages apply. Indeed, motor impairment is even worse than in the hand block, because at times the patient can experience much difficulty with walking after a nerve block of both feet.

New anesthetic procedure combining lidocaine iontophoresis with cryotherapy
Because of the long list of side effects associated with nerve blocks, many different modalities for regional anesthesia have been tried by the author, including cooling sprays and EMLA® cream under occlusion for one hour or more. The cooling spray technique produces an unpleasantly frozen hand, both for the patient and the treating doctor. Furthermore, there is only a moderate anesthetic effect, particularly for the burning pain experienced during the injection of the solution (it is less for the needle stick). EMLA® cream under occlusion for one hour or more gives an excellent anesthetic effect for the stinging of the needle, but only minimal relief from the burning experienced during the injection of the fluid. Moreover, the topical application of an anesthetic cream with occlusion for one hour produces maceration and swelling of the hand, which makes it extremely difficult to find the correct depth to inject the BOTOX®, which must be intradermal and not subdermal. It is imperative to remain intradermal with injections of BOTOX® for palmar hyperhidrosis, especially if muscle weakness is to be avoided.
A report on topical dermal analgesia induced by iontophoretic administration of 2 per cent lidocaine\(^1\) led the author to perform a new form of anesthesia for the treatment of palmoplantar hyperhidrosis with BOTOX\(^2\). This new technique achieves almost complete anesthesia with only slight stinging and burning, similar to what is felt during injections of BOTOX\(^*\) for axillary hyperhidrosis\(^2\). Initially, this new technique was performed using only iontophoresis with 2 per cent lidocaine for 30 minutes (15 minutes for each extremity) (Figure 10.9). This reduced the stinging and burning sensation but did not abolish it completely, owing
to the very superficial nature of the anesthesia. As this author’s use of the new technique grew, a combined procedure was developed which now combines the spraying of a controlled amount of liquid nitrogen cryotherapy with the lidocaine iontophoresis (Figures 10.10 and 10.11). The lidocaine solution used for iontophoresis is ordered from a local pharmacy in large quantities (e.g. 5 liters of lidocaine hydrochloride 100 g in aqua conservans 4900 g). The iontophoresis unit used is the HIDREX GS (from HIDREX, Wuppertal, Germany), which can generate a current of 15 to 25 mA (Figure 10.9). The hand should be covered by the lidocaine solution until the back of
the hand is submerged, as is usually done for antihyperhidrotic iontophoretic therapy (Figure 10.4).

This new combination iontophoresis/cryotherapy technique has the advantage of specifically dosing a focus of liquid nitrogen cryotherapy in such a manner that it does not cause the entire hand to freeze. Just before BOTOX® is injected, the site to be treated is sprayed with liquid nitrogen cryotherapy until a faint white spot appears (Figure 10.11). The BOTOX® then is injected directly into this focus of partially frozen anesthetized skin (Figure 10.11). With this technique a pain-free vertical injection can be achieved, even on the fingertips.

This new combined iontophoresis/cryotherapy technique was used to produce anesthesia prior to BOTOX® injection in the palmo plantar surface in an experimental group of 36 patients. The technique resulted in an overall satisfaction rate in 92.3 per cent of all patients, compared to only 37.8 per cent in a group treated with EMLA® and 17.8 per cent in a group treated with the nerve blocks. The low level of satisfaction after nerve block is due not to the poor anesthetic effect, but to the severe side effect profile of this technique (see above). However, there is also an unpleasant side effect with the combined iontophoresis cryotherapy technique, i.e. liquid nitrogen often produces mild blistering at the application site when a small-one hole treatment cone is used (Figure 10.12). This blistering was never a severe medical problem, but was a source of embarrassment for some patients.

Different nozzles and cones are available for cryotherapy, but they all have a one-hole exit port. Moreover, the diameter of the cone or nozzle should be as small as possible to achieve precise anesthesia (Figure 10.12). However, it is inevitable that while this combined anesthetic technique is performed some sites will blister. Therefore the author has developed a new cooling system for liquid nitrogen cryotherapy using a 10-hole nozzle (Figure 10.13). This nozzle was initially produced to create a comfortably cool haze after laser therapy. The 10-hole nozzle produces a defocused iced spray that produces complete anesthesia without any blistering. Although this combined technique requires some training and an assistant to perform (the assistant cools, the physician injects), this technique is highly recommended owing to increased patient satisfaction.
Applications for BOTOX® injections in rare forms of focal hyperhidrosis

Along with the common occurrence of primary localized hyperhidrosis of the palms, soles, or the axillae, there are rare forms of focal hyperhidrosis that can also be treated with injections of BOTOX®. Some of these cases are classified as primary focal hyperhidrosis (hyperhidrosis of the forehead and inguinal area), some are associated with syndromes (Ross syndrome, Frey syndrome), and others are iatrogenic side effects and complications of surgical procedures, such as ETS (i.e. compensatory hyperhidrosis) and still others are idiopathic entities such as localized unilateral hyperhidrosis (LUH).

Primary focal hyperhidrosis of the forehead and anogenital area

Even though these localizations of focal primary hyperhidrosis are not as common as axillary or palmoplantar hyperhidrosis, it is very important to provide treatment for them. Patients can experience serious emotional stress and intense social embarrassment when they find themselves dripping sweat from their forehead down into their face, or when they find the need...
to wear panty liners to prevent profuse sweating from saturating their pants and trousers caused by inguinal and perineal hyperhidrosis.

The principles of treatment of the anogenital area remain the same as in other localizations of focal hyperhidrosis. The first stage of therapy should be attempted with the application of aluminum salt solutions. This often achieves a satisfactory result and nothing else has to be done. ETS has been suggested for therapy-resistant severe focal hyperhidrosis of the forehead. However, this procedure is associated with an even higher risk of severe and widespread compensatory hyperhidrosis (see Figure 10.5), more so than with ETS for palmar hyperhidrosis. This is probably due to the huge area of attendant anhidrosis (of the head, back, breast, and shoulders) resulting from ETS. The treatment of compensatory hyperhidrosis is very complicated (see below). ETS for the lower limbs, including the inguinal area and perineum, is not recommended as a standard procedure, owing to technical difficulties in performing it laparoscopically. Systemic treatments such as anticholinergics, sedatives or tranquillizers - with or without combination therapy with beta-blockers - are neither very effective nor well tolerated by patients, because of the associated side-effects. Therefore, if aluminum salts are not effective, BOTOX® injections should be considered as a second-line treatment and surgical treatment reserved only for selected cases. However, there are cases of huge areas of hyperhidrosis affecting not only the forehead, but the whole face, the back, the breasts, chest, and the shoulders, when oral anticholinergics may be effective before BOTOX® injections are even considered.

Botulinum toxin injections for hyperhidrosis of the forehead and anogenital areas

In most cases of hyperhidrosis of the forehead, patients sweat profusely at the hairline. Owing to the involvement of the underlying frontalis, BOTOX® should not be injected within 1.5–2.0 cm of the eyebrows to prevent the occurrence of either brow ptosis, or blepharoptosis, or both. For the same reason, the dilution of the BOTOX® should be much less than that which is used for axillary hyperhidrosis. To prevent any diffusion beyond the target area, low doses (approximately 2 U per injection point) (see above) and low-volume dilutions (2.5–5.0 ml) of BOTOX® should be used. However, dilutions of 5 ml per vial of BOTOX® can be used without adverse sequelae if the proper technique is used. With such high-volume BOTOX®, the risk of producing a ‘heavy
forehead or brow ptosis for a few days or weeks is increased. However, therefore a dilution with 4 ml or even 2.5 ml per vial of BOTOX® is recommended for treatment of the forehead. As with other areas, it is important to perform a Minor starch test before the injection points are marked on the surface of the forehead (Figure 10.14).

In sharp contrast to BOTOX® injections in the forehead, the dilution of BOTOX® when treating inguinal hyperhidrosis (Figure 10.15) should be as high as possible to achieve maximum diffusion, since the areas of hyperhidrosis in the anogential area can be quite extensive. However, the rule of injecting 2 U per site remains the same in this indication. The injection technique in principle is similar to the way other areas of focal hyperhidrosis are treated, but it is very important to perform the injections intradermally to prevent paralyzing the muscles of the pelvis. Therefore this procedure should only be performed by experienced practitioners.

Hyperhidrosis associated syndromes

Several rare syndromes associated with hyperhidrosis are described in the literature: POEMS syndrome, pachyonychia congenita, Apert syndrome, pachydermoperiostosis, Papillon–Lefèvre syndrome, nail-patella syndrome, etc. Only two syndromes that can be treated with BOTOX® will be discussed here.

Frey syndrome

Gustatory sweating is a common complication following parotid gland surgery, infection, or trauma. It was first described by Lucie Frey in 1923. The most likely explanation for the condition is a misdirected resprouting of postsynaptic salivomotor parasympathetic fibers that
have lost their glandular target organ. Following gustatory stimulation, the clinical picture (Figure 10.16) includes pathological sweating of the preauricular area and sometimes a flushing reaction involving the superficial cutaneous vasculature. About 50 per cent of patients experience gustatory sweating after parotidectomy and 15 per cent consider their symptoms severe47. BTX-A (BOTOX®, Allergan Inc, Irvine, CA) is an effective therapeutic option for the treatment of gustatory sweating and it can be considered as a first-line treatment. The duration of treatment effect in patients with Frey syndrome is much longer than in patients treated for other indications, such as hemifacial spasm or blepharospasm or even hyperhidrosis in other areas (mean duration 17.3 months)48.

Ross syndrome

Ross syndrome was first described by the neurologist Alexander T. Ross in 195849. It is characterized by the triad of unilateral tonic pupils, generalized areflexia (Holmes–Adie syndrome), and progressive segmental anhidrosis with a compensatory band of excessive perspiration. Patients suffering from Ross syndrome usually do not perceive the hypohidrosis; instead, it is the compensatory segmental hyperhidrosis that is bothersome. In addition, many patients suffer from several symptoms of vegetative dysfunction, such as palpitation, stenocardia, orthostatic hypotonia, and irritable colon45. The pathogenesis of Ross syndrome is unknown. Multiple neuropathies of the autonomic nervous system or a failure in the synthesis or release of neurotransmitters have been suggested as possible causes49. There is no histologic evidence of nerve fiber destruction. Therefore Ross postulated a defect in acetylcholine cholinesterase activity, rather than the degeneration of sweat glands. The progression of Ross syndrome is very slow. There is no therapy for the segmental progressive anhidrosis. The bothersome compensatory hyperhidrosis can be improved, however, with systemic antimuscarinic drugs or with injections of BOTOX® into the affected areas, usually the face. In 1992 Itin et al.50 presented a case study of a patient suffering from Ross syndrome with a defined area of anhidrosis in the right hand, the right axilla, and the right side of the face. In follow-up, after 11 years the patient presented with additional anhidrotic areas in the right hemithorax and the underside of the left arm (Figure 10.17). Unfortunately the patient refused treatment with BOTOX®, even though the hyperhidrosis was so severe that electrolyte replacement was necessary (unpublished data).
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Treatment of compensatory hyperhidrosis after endoscopic thoracic sympathectomy (ETS)

Compensatory hyperhidrosis can be a very embarrassing, almost a disabling disease. The incidence after ETS is relatively high (see above); severe problematic cases with generalized severe sweating are fortunately rare. The treatment options for patients with copious sweating of almost the entire body are very limited. One possibility is the use of anticholinergic drugs, with their attendant adverse side effects. BOTOX® treatment is limited by the potential toxic side effects associated with the high doses required (estimated LD₅₀ of a human being is 3500–5000 U) and the expense of treating such large involved areas (Figure 10.5). BOTOX® therapy in such cases does not seem to be as effective as it is when treating focal hyperhidrosis, i.e. axillary or palmoplantar hyperhidrosis. A further limiting problem is suppressing excessive sweating without the risk of hyperthermia. Under these circumstances, the aim of each individual therapy should be to combine several therapeutic modalities to achieve the best outcome. The patient should be aware of the difficulties in treating such conditions and should be counseled to be satisfied with the reality of achieving moderate success. An algorithm that can be used in treating such cases is, first, the application of aluminium salt solutions, combined with the ingestion of anticholinergic drugs in an ever-increasing dosage, as the mandatory first line of
treatment. A few patients will need additional therapy for well-defined areas of intensely active sweating. Such cases will benefit from injections of BOTOX®. Again it is most important to define the affected areas of hyperhidrosis by the use of the Minor starch test (Figure 10.18) Then BOTOX® can be injected as described above (Figure 10.19).

Localized unilateral hyperhidrosis

Localized unilateral hyperhidrosis (LUH) is a rare form of idiopathic localized hyperhidrosis and is defined as a confined area of hyperhidrosis of less than 10 × 10 cm, mainly found on the forehead or the forearm, whose pathogenesis is unknown (Figure 10.20). Beside the unusual localization, the major difference from essential hyperhidrosis is that LUH has no typical triggering factor and occurs even while patients are asleep. The etiology of LUH is unknown but may be due to a misdirected reconnection of the sympathetic nerve fiber network after injury, similar to the Frey syndrome1. Before BOTOX®, no treatment was available for this distinctive but enigmatic skin disorder. However, excellent results have been experienced following injection of 30 units of BOTOX® in a patient suffering from LUH1.
References


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