AAD 1938 DERMATOLOGY

AMERICAN ACADEMY OF DERMATOLOGY

VOLUME 20 NUMBER 5 PART 1 MAY 1989

Continuing medical education

Biology of sweat glands and their disorders. II. Disorders of sweat gland function

K. Sato, W. H. Kang, K. Saga, and K. T. Sato *Iowa City, Iowa*

Part I of this article (J AM ACAD DERMATOL 1989;20:537-63) focused on normal sweat gland function. Part II provides a discussion of hyperhidrosis and hypohidrosis. Hyperhidrotic disorders affect the palms and soles and the axillae and are associated with previous spinal cord injuries, peripheral neuropathies, brain lesions, intrathoracic neoplasms, systemic illness, and gustatory sweating. Hypohidrotic disorders include anhidrotic ectodermal dysplasia, hereditary sensory neuropathy, Holmes-Adie syndrome, and generalized anhidrosis. (J AM ACAD DERMATOL 1989;20:713-26.)

HYPERHIDROSIS

Hyperhidrosis of the palms and soles

Excessive sweating, especially of the palms and soles, is a socially and an occupationally distressing, and sometimes disabling, condition. Although numerous publications are available on this subject, most of them focus on therapy rather than the pathophysiology of the problem. Sweat glands on the palms and soles are activated predominantly by emotional stimuli. These glands, however, do not differ significantly—morphologically, pharmacologically, or neurologically[1]—from those on the hairy skin surface. It has been speculated that the hypothalamic sweat center that controls the palms and soles (and axilla in some patients) is distinct from the rest of the hypothalamic sweat centers and is under the exclusive control of the cortex without input from the thermosensitive elements. Thus emotional sweating never occurs during sleep or sedation. Of interest is a recent study by Momose et al.,[2] which revealed that the electroencephalographs of patients with hyperhidrosis of the palms and soles show abnormalities such as sharp wave bursts during challenge by hyperventilation, and their frontal cortexes take up an increased amount of a marker, *N*-isopropyl I-123 *p*-iodoamphetamine, which the authors interpreted as reflecting hyperperfusion of the frontal area.

Shih et al.[3] studied autonomic functions in normal subjects, in those with hyperhidrosis of the palms and soles, and in those who had had T2-T3 ganglionectomy. Compared with normal subjects and those with hyperhidrosis, the subjects whose ganglia had been excised showed a much smaller sweating response of the forehead, the upper portion of the chest, and the arms. A much greater (presumably compensatory) sweating response, however, was observed both in the lateral lumbar and in the ventral thigh regions in response to body exercise. Subjects with hyperhidrosis had less reflex bradycardia than the other groups in response to Valsalva's maneuver or face immersion, but they showed a higher degree of cutaneous vasoconstriction in response to finger immersion in cold water. The observation was interpreted to indicate over-

From the Marshall Dermatology Research Laboratories, University of Iowa College of Medicine.

Supported in part by National Institutes of Health Grants Nos. DK27857, HL32731, and AR25339 and Cystic Fibrosis Foundation No. G124.

Reprint requests: Kenzo Sato, MD, Marshall Dermatology Research Laboratories, University of Iowa College of Medicine, Iowa City, IA 52242.

functioning of the sympathetic nervous fibers in subjects with hyperhidrosis and the increase of sympathetic outflow passing through the T2-T3 ganglia that causes palmar hyperhidrosis.[3]

Excessive palmoplantar sweating induces hypothermia of the hands and fingers by evaporative cooling, which may then increase the sympathetic outflow because of the aforementioned sympathetic reflex and thus further aggravate hyperhidrosis. It is of interest that successful treatment of palmoplantar hyperhidrosis elevates the palmar skin temperature by 2.5° C,[4] which also may help alleviate the vicious cycle of sympathetic reflex. Palmoplantar hyperhidrosis has been reported to occur in some (but not all) patients with nail-patella syndrome,[5] keratosis palmaris et plantaris with clinodactyly,[6] Raynaud's disease, erythromelalgia, atrioventricular fistula, cold injury, and rheumatoid arthritis.[7] Cloward[8,9] reported that palmar hyperhidrosis develops 20 times more often in Japanese Americans living in Hawaii than in Hawaiian residents of non-Japanese ancestry. His assumption is based on the observation that of his own 82 patients with palmar hyperhidrosis between 1938 and 1956, 66 (80%) were of Japanese ancestry, and half of these were of Okinawan origin.[8,9] Unfortunately, no subsequent studies have been published on the frequency of palmar hyperhidrosis among the Hawaiian population or among Japanese in Japan.

During the past 40 years, tap water iontophoresis has been established as the most effective, safe, and inexpensive therapeutic modality for palmoplantar hyperhidrosis.[4,10,11] At present a number of iontophoresis units are commercially available.[12] In our experience any instrument that can deliver as much as 20 mA of direct current may be satisfactory. Treatment of each palm (or sole) for 30 minutes at 15 or 20 mA daily in tap water usually induces significant hypohidrosis within a week. Because the efficacy of galvanic current is roughly a function of total electric power (i.e., current × duration), the use of power supplies with lower power output either requires much longer treatment time or results in an inadequate therapeutic response.

The mechanism by which tap water iontophoresis stops sweating is unknown, although poral plugging by poral hyperkeratosis in the forearm skin was speculated as its mechanism almost 40 years ago by Shelley et al.[13] Two puzzling observations are that iontophoresis in normal saline solution is not as effective as in tap water and that the anode is more effective than the cathode.[14] In aqueous solutions the electric current always is carried by charged ions. Thus it is an open question as to why plain water is more effective than salt solutions. The answers to these puzzles, if clarified, may provide clues to the mechanism of the anhidrotic effect of tap water iontophoresis.

If tap water iontophoresis is ever unsuccessful, the last resort may be thoracic sympathectomy. (During the past 10 years at the University of Iowa Dermatology Clinic we have experienced only successful results in our 50 patients.) Patients should be informed, however, of the potential side effects of sympathectomy (e.g., Horner's syndrome, pneumothorax, postsympathetic neuralgia, phrenic nerve paralysis, dorsal scapular neuralgia, compensatory hyperhidrosis in other parts of the body, and stuffy nose) and the possibility of treatment failures.[15] Although improved techniques of sympathectomy have reduced the incidence and severity of side effects,[16-18] they are nonetheless invasive, irreversible, expensive, and not without side effects.

Hyperhidrosis of the axillae

In Part I of this article (see the April issue of the JOURNAL) the presence of apoeccrine sweat glands and their major contribution to overall axillary sweating rate are described. It is our experience that those patients with excessive axillary sweating rarely have excessive axillary odor and rarely are regular users of commercial antiperspirants. Thus suggests either that precursors of odor-producing materials derived from the apocrine glands are washed off by excessive sweating or that the secretory activity of eccrine and apoeccrine glands does not parallel that of the apocrine glands.

The emotional nature of axillary sudomotor function (supplied mainly by the fourth thoracic ganglion) is similar to that on the palms and soles except that axillary sweat glands also respond to thermal stimuli to a varying extent. Of interest is that only 25% of patients with axillary hyperhidrosis also have palmoplantar hyperhidrosis.[19] Unlike palmar sweating, axillary sweating is controlled relatively easily by 25% aluminum chloride in alcohol solution (Drysol) applied at bedtime[20] but without subsequent occlusion.[21] Irritation of the skin, if any, is minimized by quick drying of the

applied aluminum solution with a hair dryer, by strict avoidance of the use of any antiperspirants during the daytime, and by the application of baking soda powder to the axilla in the morning to neutralize the aluminum chloride still present on the skin (and to offer a mild deodorant effect). If irritation of the axillar skin still persists, we then have the patients apply white petrolatum (Vaseline), or 1% hydrocortisone in Vaseline, to the axilla about 2 to 3 hours before application of aluminum solution to provide an additional barrier layer on the stratum corneum.

Although all our patients at the University of Iowa Dermatology Clinic responded satisfactorily to this protocol, should treatment with topical aluminum fail, tap water iontophoresis with a special axillary electrode,[22] resection of axillary skin,[19] or the subcutaneous liposuction technique[23] may be considered. Again, thoracic sympathetectomy (usually second through fourth thoracic ganglia), which is also effective,[24] should be considered only as a last resort.

Localized hyperhidrosis associated with previous spinal cord injuries

In theory, injuries to the spinal cord should result in sudden loss of sweating below the level of the lesion when exposed to thermal stimuli. In contrast, local sweating caused by intradermal cholinergic agents gradually disappears within a few weeks to several months when postganglionic fibers are damaged, compared with the several months to 2 years required when sympathetic fibers are severed at the preganglionic level.[25] Some patients with spinal injuries, however, experience episodes of profuse sweating months or years after injuries in the skin areas outside the sensory or autonomic dermatomes. Although the mechanism of hyperhidrosis is not always clear, these cases may be separated into three major groups: (1) those associated with autonomic dysreflexia,[26-28] (2) those triggered by orthostatic hypotension,[29] and (3) those caused by posttraumatic syringomyelia.[30,31]

Hyperhidrosis associated with autonomic dysreflexia. This syndrome occurs in patients with spinal cord lesions at or above the sixth thoracic level (T6). It is characterized by exaggerated autonomic responses to stimuli such as bowel and bladder distention, visceral inflammation, and skin irritation and pain that are innocuous in unaffected persons. The clinical triads include episodic onset of profuse sweating on the face, neck, and upper portion of the trunk; vasodilation resulting in flushing of the face and congestion of the nasal passages; and a throbbing headache. In addition, other signs of sympathetic hyperactivity, such as piloerection and hypertension, and hyperparasympathetic symptoms, such as bradycardia with vasodilation, occasionally are present.[26-28]

The pathogenesis of autonomic dysreflexia is still unknown. It has been speculated, however, that the afferent stimuli from the bladder or bowel travel to the spinal cord in the caudal stump, causing reflex arteriolar spasm of the skin and splanchnic vessels by means of the efferent sympathetic motor fibers and thus resulting in severe paroxysmal hypertension.[27] The subsequent vasodilation (and bradycardia in some patients) may be compensatory in nature and most likely is mediated by stimulation of parasympathetic activity through the carotid and aortic bodies, although such a compensatory reaction usually fails to reduce blood pressure significantly.

The mechanism of hyperhidrosis in autonomic dyreflexia (usually above the spinal lesions) is not well understood. The beneficial effect of oral propoxyphene hydrochloride (Darvon) on hyperhidrosis in autonomic dyreflexia has been reported in a few patients.[28] Because Darvon is a narcotic with a weak ganglion-blocking effect, Tashjian and Richter[28] speculated that hyperhidrosis in autonomic dyreflexia may be due to interruption (by spinal lesions) of inhibitory impulses from higher centers (whereas Darvon blocks the remaining stimulatory impulses). The answers to the questions of why the onset of autonomic dyreflexia varies from several weeks to 13 years after spinal injury and why it occurs only in certain patients also are unknown. The slightly increased plasma norepinephrine levels resulting from increased reflex sympathetic outflow, coupled with denervation hypersensitivity of catecholamine receptors, also may contribute to the pathogenesis of autonomic dyreflexia.[28] The differential diagnosis of autonomic dyreflexia includes pheochromocytoma, toxemia of pregnancy, intracranial posterior fossa neoplasms, migraine, cluster headaches, and primary hypertension.[28]

Hyperhidrosis resulting from orthostatic hypotension. This form of hyperhidrosis occurs in some patients months to many years after cervical spinal cord transection, although orthostatic hypo-

tension alone can occur immediately after the cord injury. Quadriplegia usually is present (from the past cervical injury), and a sudden spell of dizziness because of orthostatic hypotension occurs when these patients tilt their heads or sit in upright positions. This is followed within 5 to 10 minutes by rising blood pressure, profuse sweating on the face, neck, and upper portion of the chest and arms, chattering of teeth, piloerection, blurred vision, and agitation. When these patients resume a supine position, symptoms improve within 10 minutes. Thus this condition may be a variant of autonomic dysreflexia except that orthostatic hypotension, instead of bladder or bowel distention, triggers a mass discharge of sympathetic neurons.[29] Fludrocortisone acetate, 0.3 mg daily, is reported to control sweating in such patients[29] although its mechanism of action is not clear.

Hyperbradykininemia. Hyperbradykininemia was reported to be involved in the mechanism of orthostatic hypotension in one family.[30] Because plasma bradykinin levels have not been studied in other cases of quadriplegia with orthostatic hypotension and hyperhidrosis, no general statement can be made regarding the role of plasma bradykinin in autonomic dysreflexia.

Posttraumatic syringomyelia. This variation of hyperhidrosis should be suspected in patients with paraplegia (caused by injuries to the spinal cord at any level) who have a recent onset of hyperhidrosis with or without progressive numbness in the hyperhidrotic areas.[31,32] Again, the onset of hyperhidrosis lags months to many years after trauma. Since syrinx (a fluid-filled cavity in the spinal cord) can develop above and/or below the level of transection (ascending and/or descending syrinx, respectively), hyperhidrosis with or without numbness of the skin also can occur in areas of the skin that correspond to above and/or below the lesion (depending on the degree of preservation of sympathetic nerves below the lesion). It is important to diagnose posttraumatic syringomyelia in such patients because syrinx can be easily diagnosed radiologically and treated by surgical draining.[32]

Hyperhidrosis associated with peripheral neuropathies

Increased sweating is reported to occur in subsets[33] of patients with hereditary sensory neuropathy, including type III (familial dysautonomia or Riley-Day syndrome).

Familial dysautonomia. This is a recessively inherited disorder, whose diagnostic criteria include lack of an axon reflex flare after intradermal injection of histamine (indicating peripheral panneuropathy), absence of fungiform papillae on the tongue, miosis of the pupil after instillation of dilute methacholine (normal subjects do not respond), diminished deep tendon reflexes, lack of overflow tears, failure to thrive, generalized reduction in pain sensation, mild mental retardation, erythematous mottling of the skin on heat exposure, and Ashkenazic Jewish ancestry.[33] The degree of hyperhidrosis may vary. The mechanism of hyperhidrosis in Riley-Day syndrome is unknown although it is speculated to result from increased excitability of the sweat center.[34]

Congenital autonomic dysfunction with universal pain loss.[33] This dysfunction is somewhat similar to Riley-Day syndrome (familial dysautonomia) except that these patients are not Ashkenazic Jews. Those affected have complete (not partial as in Riley-Day syndrome) sensory loss with accidental self-mutilation and corneal opacities, profound hypotonia, episodic fever, and frontal bone prominence.

Cold-induced profuse sweating. Onset of profuse sweating in the neck and on the thorax, aggravated by cold weather or nervousness, has been reported in two sisters with peripheral motor neuropathy with autonomic dysfunction.[35] Their symptoms began in early childhood, and the patients also noted slowly progressive muscular weakness and hypotrophy (caused by demyelination of motor nerves), distal cyanosis, orthostatic hypotension, and esophageal achalasia; sensory neuropathy, however, was absent.[35]

Hyperhidrosis associated with brain lesions

A variety of lesions in the brain can cause episodes of profuse sweating, but they can be separated into two major groups: those associated with hypothermia and those not associated with hypothermia.

Episodic hypothermia with hyperhidrosis. First reported by Hines and Bannick,[36] this disorder can begin at any age (usually 9 months to 38 years) in apparently normal persons or in patients with a history of seizures, mental retardation, polydipsia, or hemiparesia.[37] Episodes of profuse sweating often follow awakening or standing up and are preceded by a generalized feeling of warmth, tingling, and flushing of the face, during which time body temperature decreases to 31° C

(or in an extreme case to 24° C). A few minutes later a sudden drenching sweat begins and lasts 5 minutes to several hours. The diaphoretic episodes, which occur more than 10 times daily in some patients or only a few times a year in others, often are associated with chills, ataxia, slowed psychomotor responses, tremors, hyperreflexia, headaches, and/or hypotonia. Hyperhidrosis in these patients most likely is due to the episodic decrease of hypothalamic temperature setpoint (which often is referred to as diencephalic epilepsy or hypothalamic storm) by diencephalic lesions or malformations such as agenesis of corpus callosum, heterotopia, microgyria, porencephalia, malformation of cranial nerves and brain-stem nuclei, cholesteatoma, lipoma, or surgical manipulation of the anterior hypothalamus.[37] Electroencephalographic examination is usually of no diagnostic help, but the lesions often can be localized by computed tomographic scans and pneumoencephalographic examination. Anticonvulsants[37] and oxybutynin[38] have been used for control of hypothermia and hyperhidrosis with variable success.

Generalized hyperhidrosis not associated with hypothermia. This form of hyperhidrosis has been reported in a patient with episodic hypertension and hypothalamic-pituitary dysfunction after brain injury[39] and in a patient after the onset of epilepsy.[40] A small cerebrovascular accident in the region of the hypothalamus was suspected as the cause of diaphoresis in the latter patient.[40]

Profuse facial sweating precipitated by perfume smells. Olfactory hyperhidrosis not precipitated by gustatory or mental stimuli was reported in a 42-year-old woman.[41] Her facial sweating was successfully treated with amitriptyline.

Idiopathic unilateral circumscribed hyperhidrosis

Unilateral circumscribed idiopathic hyperhidrosis is an uncommon condition but occasionally has been reported in the dermatologic literature during the past 40 years.[42-46] The hyperhidrotic area usually is sharply demarcated, measuring no larger than 10×10 cm^2, and it is present mainly on the face and arms of an otherwise healthy person (Fig. 1). The age at onset varies between 7 and 67 years, and patients typically notice sudden onset of profuse sweating precipitated by heat, which lasts 15 to 60 minutes. In some patients, mental or gustatory (in the case of facial unilateral circumscribed hyperhidrosis) stimulation also triggers sweating.

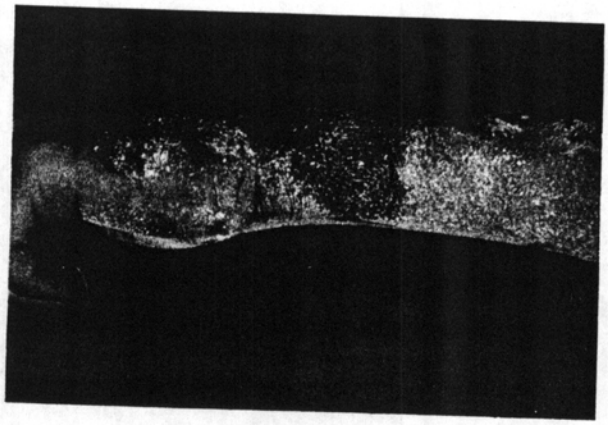

Fig. 1. Idiopathic unilateral circumscribed hyperhidrosis in a 7-year-old boy visualized by the conventional iodine starch method. The sweating attack is precipitated by heat but also occurs spontaneously in this patient.

The attacks occur more frequently in summer than in winter. Characteristically, there is no accompanying sensory or motor neuropathy, flushing of the face, headaches, excessive salivation, lacrimation, vasodilation, or piloerection.

The pathogenesis of unilateral circumscribed hyperhidrosis is unknown. The increased sweat rate in response to intradermal cholinergic agents[42, 45] and hypertrophy of the glands on biopsy specimens[42, 44] have been reported, although sweat glands in some patients show apparently normal histologic findings.[43] It is not clear whether glandular hypertrophy represents functional hypertrophy resulting from repeated episodes of sweating or whether local tropic factors (e.g., epidermal growth factor[47] or other factors) are primarily involved, rendering the sweat glands more sensitive to endogenous pharmacologic stimulation. Long-term follow-up of these cases has not been reported. However, localized hyperhidrosis in the patient shown in Fig. 1 has gradually subsided during a period of 2 years. Sweating may be partially controlled by local application of 25% aluminum salts, topical anticholinergic agents, or systemic clonidine.[46] As a last resort, total excision of the affected skin area should be considered.

Paroxysmal unilateral hyperhidrosis associated with intrathoracic neoplasms

Abnormal thoracic sympathetic activity caused by encroachment of a tumor (e.g., pulmonary adenocarcinoma, bronchial carcinoma, and methothelioma) on the sympathetic trunk or postganglionic fibers can cause unilateral (usually ipsilateral)

hyperhidrosis.[48-51] Likewise, pressure from benign lesions such as cervical rib or osteoma on the sympathetic chain also can cause hyperhidrosis on the ipsilateral face, neck, and chest. Hyperhidrosis often is preceded by other signs of internal malignancy such as chest pain, dyspnea, weight loss, and lymphadenopathy and disorders of the nervous system such as loss of sensation, weakness of facial muscles, and Horner's syndrome. Sweating is usually spontaneous, profuse, and unrelated to eating, hunger, urination, bowel movement, sleep, or physical activities. Irradiation of tumors may induce transient relief of hyperhidrosis.

Generalized hyperhidrosis associated with systemic illness

The following conditions have been reported to be associated with hyperhidrosis, although many of the reports are based only on the clinical impression of the observers or the subjective sensation of the patients and thus diagnosed without measurement of sweat rate. Disorders include **diabetes mellitus, congestive heart failure, thyrotoxicosis, hyperpituitarism, anxiety, and menopausal state disorder.** According to the study by Allen et al.[52] a significantly increased sweat rate could not be found either in experimental thyrotoxicosis or in hyperthyroid cases. In one study of **Parkinson's disease** an increase in pharmacologic sweating was noted.[53] Other studies,[54,55] however, noted a combination of patchy areas of anhidrosis and areas of hyperhidrosis, suggesting both dysfunction of the autonomic nervous system and secondary compensatory hyperactivity. The symptomatic triad of excessive and inappropriate sweating, tachycardia, and headaches (in hypertensive patients) almost ensures (94%) the diagnosis of **pheochromocytoma.**[56] Further confirmational test results include increased urinary catecholamine excretion (especially total methanephrines) and plasma catecholamine levels and positive findings on glucagon stimulation (the increase in plasma catecholamine by glucagon) and clonidine reaction (plasma catecholamine level decreases).[56] **Generalized hyperhidrosis precipitated only by emotional stimulation**[57,58] and **cold-induced hyperhidrosis**[59] have been reported, but their pathogeneses are unknown. Excessive diaphoresis also has been reported as a side effect of antidepressants such as cyclobenzaprine (Flexeril)[60] and fluoxetine.[61]

Localized hyperhidrosis associated with cutaneous diseases

Localized hyperhidrosis has been seen in the skin over the **blue rubber bleb nevus** (presumably caused by axon-reflex sweating after manipulation of the painful lesion),[62] in the perilesional skin in 8 or 10 cases of **glomus tumor** (presumably a result of increased local temperature and/or pain)[63] and in association with **POEMS syndrome** (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, and *s*kin changes),[64] **Gopalan's syndrome** (burning feet syndrome),[7] **causalgia,**[7] and **pachydermoperiostosis.**[65] Association of local sweating with these and other cutaneous lesions may be either a rare coincidental phenomenon or a result of axon-reflex sweating. In fact, occurrence of beads of sweat around painful ulcers (presumably caused by axon reflex) is not a rare occurrence in daily dermatologic practice.

Hyperhidrosis in gustatory sweating

Physiologic gustatory sweating occurs in normal persons while they are eating certain hot spicy foods. It is relatively mild and occurs symmetrically around the lips, nose, and forehead. Although pathologic gustatory sweating also is precipitated by gustatory stimulation (but not by merely thinking of foods), it is usually unilateral involving the preauricular or infraauricular areas of the face. It can be mild or embarrassingly profuse. Pathologic gustatory sweating can be classified into several types according to cause: (1) gustatory sweating as a result of hyperactivity of sympathetic function associated with encephalitis or syringomyelia[66] (both very rare), invasion of the cervical sympathetic trunk by tumor[67] (as in Pancoast's syndrome), or sympathectomy (seen in 73% of patients with sympathectomy, presumably caused by aberrant regeneration of nerves; Horner's sign also may be present)[68,69]; (2) gustatory sweating associated with peripheral autonomic and sensory neuropathy as in diabetes mellitus[70] and herpes zoster of the preauricular area[71]; (3) gustatory sweating caused by parotitis or parotid abscess (very rare); and (4) auriculotemporal (Frey's) syndrome.

Frey's syndrome occurs in 37% to 100% of patients 1 month to 5 years after surgery or injury on or about the parotid gland.[72-75] The syndrome results from injury to the parotid gland and/or

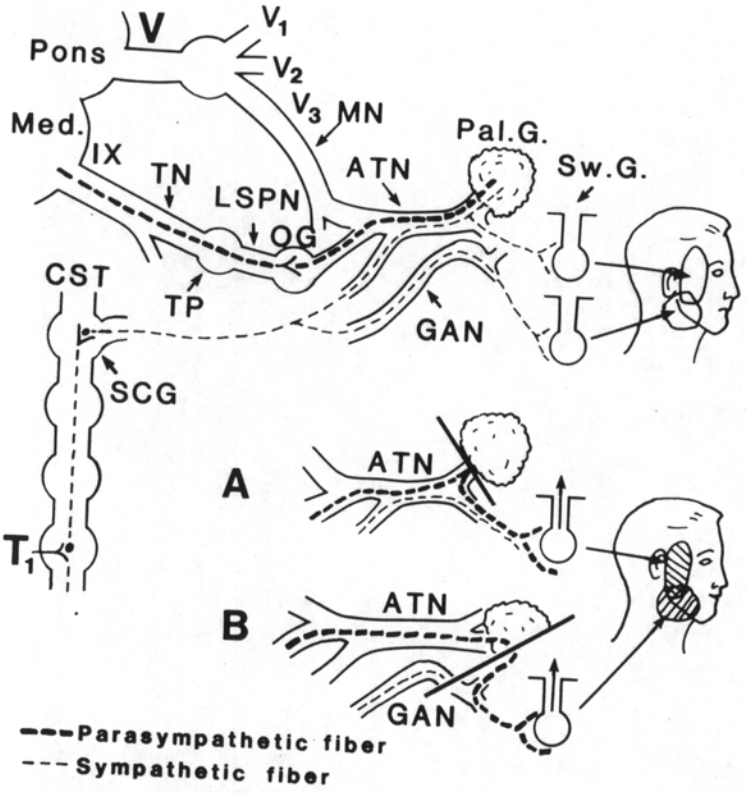

Fig. 2. Schematic illustration of parotid secretomotor and sudomotor neural pathway. *Med.*, Medulla oblongata; *V*, trigeminal nerve; *MN*, mandibular nerve; *ATN*, auriculotemporal nerve; *IX*, glossopharyngeal nerve; *TN*, tympanic nerve (or Jacobson's nerve); *TP*, tympanic plexus; *LSPN*, lesser superficial petrosal nerve; *OG*, otic ganglion; *GAN*, greater auricular nerve; *Pal. G*, parotid gland; *Sw. G*, sweat gland; *CST*, cervical sympathetic trunk; *SCG*, superior cervical ganglion; T_1, first thoracic nerve. *A* and *B*, The most widely held "misdirection" hypothesis on the pathogenesis of Frey's syndrome, that is, injury to the parotid gland and/or auriculotemporal nerve (as indicated by *diagonal line*), causes misdirection of its parasympathetic fibers toward the sweat glands in the preauricular area *(A)*. When both the greater auricular nerve *(GAN)* and the parotid gland are severed, the regenerating parasympathetic fibers from the *ATN* migrate into *GAN* to reach the sweat glands, causing gustatory sweating in the infraauricular area *(B)*.

auriculotemporal nerve, which carries sensory fibers from the skin and parasympathetic and sympathetic fibers to the sweat glands within its distribution (Fig. 2). According to the misdirection hypothesis the severed parasympathetic fibers in the auriculotemporal nerve regenerate and migrate into the postganglionic sympathetic fibers to reach the sweat glands, as well as the blood vessels, in the preauricular area (Fig. 2, *A*). When the greater auricular nerve is damaged together with the parotid gland, the parasympathetic fibers regenerating from the damaged parotid gland migrate into the distal segment of greater auricular nerve to innervate the sweat glands in the infraauricular area (Fig. 2, *B*). The validity of the misdirection theory is supported because surgical destruction of the tympanic plexus abolishes gustatory sweating in patients with Frey's syndrome. Destruction of the tympanic nerves thus has been used for surgical treatment of excessive sweating in some patients.[76] Gustatory sweating in Frey's syndrome is usually mild; that is, only 10% of patients may require various forms of treatment. Topical scopolamine cream (3% to 5%) and 20% aluminum chloride in ethanol have been used with variable success.[75, 77] Injecting alcohol around the auriculotemporal nerve has been reported to eliminate symptoms for several months.[75] Tympanic neurectomy[76] and an

interpositional fascia graft[78,79] may offer permanent relief.

Gustatory sweating in diabetes mellitus. Bilateral and widespread facial sweating may occur and thus may represent exaggerated physiologic gustatory sweating. However, because this condition is often painful, and abnormal sprouting of unmyelinated fibers has been observed in such painful lesions, Bronshvag[80] speculated that axonal degeneration of the parasympathetic fibers with abnormal sprouting into the sympathetic fibers may be involved as its pathogenesis. Clonidine has been reported to control sweating in a patient with diabetic gustatory sweating.[81]

Gustatory sweating associated with upper dorsal sympathectomy. This variant of gustatory sweating is explained on the basis of preganglionic sympathetic regeneration or collateral sprouting with aberrant synapses in the superior cervical ganglion.[69] This is of interest because ipsilateral gustatory sweating occurs in the presence of other Horner's signs (note that full Horner's syndrome includes ipsilateral anhidrosis of the face), but sweating is more intense in their absence.[81]

The cause of so-called **lacrimal sweating** (continuous profuse sweating in the right supraorbital region) associated with **Raeder's paratrigeminal syndrome**[82] (Horner's signs plus temporal and frontal headache on the right) is unknown.

Hyperhidrosis in nocturnal diaphoresis (night sweats)

The pathogenesis of night sweats is unknown, but they can be associated with tuberculosis, endocarditis, lymphoma, hyperthyroidism, diabetes mellitus, hypoglycemia caused by insulin overdose or insulinoma, systemic vasculitis, pheochromocytoma, carcinoid syndrome, drug withdrawal, dysautonomic states, other chronic infectious diseases, dumping syndrome, acromegaly, or Prinzmetal angina.[83] A beneficial effect of indomethacin in a case of apparently idiopathic night sweat was reported in one patient,[84] but similar reports have not appeared since 1982. Treatment of the underlying disorders, if known, is of primary importance. The presence of sweating during sleep readily rules out the emotional nature of sudomotor activity. Continuous recording of rectal temperature before and after the onset of night sweats will help determine whether the decrease in hypothalamic temperature setpoint is the cause of such night sweats.

HYPOHIDROSIS (ANHIDROSIS)

Anhidrosis is the inability to produce or deliver sweat to the surface of the skin in the presence of appropriate stimuli. Thus anhidrosis should reflect dysfunction of one or more of the processes in normal neurophysiologic, anatomic, and biochemical mechanisms of sweat secretion, ranging from the function of cerebral cortex, hypothalamic sweat center, sympathetic innervation, stimulus secretion coupling, and ultimately, the patency of the sweat pores. Some of the most common causes of anhidrosis encountered in clinical practice are described in the following paragraphs.

Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)

Anhidrotic (or hypohidrotic) ectodermal dysplasia is usually, but not always, an X-linked recessive disorder characterized by decreased or absent sweating, hypotrichosis, abnormal conical teeth, saddle nose, and prominent forehead. Additional, less consistent symptoms include nail dystrophy, hyperkeratosis of palms and soles, cleft palate, hyperplasia of sebaceous glands on the face, susceptibility to eczema resembling atopic dermatitis, dryness of the mouth and eyes, and hypoplasia of mucous and mammary glands.[85-87] Hypohidrosis in anhidrotic ectodermal dysplasia results from congenital absence or paucity of the sweat glands over all the skin surface, including the palms and soles. Histologic demonstration of the absence of sweat glands[88] provides a diagnostic clue. Palmar skin biopsy is especially useful for prenatal diagnosis[89] or diagnosis in small infants with episodes of unknown fever (caused by defective thermoregulation), because other clinical signs of anhidrotic ectodermal dysplasia such as sparse hair, teeth defects, and saddle nose are rather difficult to determine in infants. Nearly 30% of these patients die in early childhood, mainly from respiratory infections.[85]

Despite the predominantly X-linked recessive inheritance of the disease, 70% to 80% of female carriers (mothers of patients) express a partial anhidrotic ectodermal dysplasia phenotype[85] such as patchy areas of hypohidrosis, sparse scalp and eyebrow hair, insufficient secretion of milk for breast-feeding, and persistence of deciduous teeth and peg-shaped teeth, which is partially explained by lyonization (random inactivation of normal X chromosomes). Accurate assessment of sweat gland density and sweating is therefore of critical

importance in detecting female carriers. Although anhidrotic ectodermal dysplasia is a heterogeneous group of disorders and more than 100 variables of ectodermal dysplasia have been recognized,[87,90] these variants are rather infrequent. They usually are distinguished by the pedigree structures and the different combinations of clinical manifestations.[91] Thus X-dominant as well as autosomal-dominant and autosomal-recessive forms have been theorized to occur,[86,87,90] but they are too numerous to enumerate here. At this writing, specific genetic markers (gene probes) are not yet available for determining the genetic inheritance of each variant[86] or for distinguishing between different heterogeneous anhidrotic ectodermal dysplasias. Differential diagnosis of this disease from progeroid syndromes such as Rothmund-Thomson, Werner's, dyskeratosis congenita, and Cockayne's syndromes is not difficult because these progeroid conditions are associated with poikiloderma, which worsens with age.[90]

Management of children and adults with anhidrotic ectodermal dysplasia is a challenge to clinicians because of the patient's heat intolerance (especially during febrile illness or physical activities and in warm climates) and susceptibility to pulmonary infections.[92] Wearing wet clothing during physical activity is partially helpful in preventing hyperthermia. It is important to note, however, that the effectiveness of external cooling is compromised in these patients because of their decreased heat transfer from the core to the skin, presumably because of the poor capillary dilation in anhidrotic ectodermal dysplasia.[93]

Congenital insensitivity to pain with anhidrosis, or hereditary sensory neuropathy (type IV) with anhidrosis

Hereditary sensory neuropathy is a relatively rare disorder, and fewer than 20 cases have been reported in the literature.[33,94-96] It is characterized by congenital generalized insensitivity to pain, generalized anhidrosis, and mental retardation. Consequently, self-mutilation, painless ulcers, fractures, and episodes of high fever predominate. The disorder is transmitted by autosomal-recessive inheritance. Although nerve biopsy specimens consistently show a lack of unmyelinated fibers and a marked reduction in the number of myelinated nerves, it is interesting that the normal number of sweat glands are present and that their morphologic characteristics are said to be normal, although the published light microscopic pictures of the sweat glands[94] appear considerably smaller than those of control specimens.

Although these sweat glands are unresponsive to local injection of pilocarpine or other cholinergic agents, an infant with hereditary sensory neuropathy type IV, a case reported by Vassella et al. in 1968,[96] responded to a combination of intradermal acetylcholine and epinephrine but was unresponsive to acetylcholine alone. A similar pharmacologic study has not been conducted by other investigators since 1968. Hereditary sensory neuropathy type IV has some similarities to familial dysautonomia (hereditary sensory neuropathy type III or Riley-Day syndrome) such as the presence of sensory neuropathy, autosomal recessive traits, and mental retardation. Unlike Riley-Day syndrome, hereditary sensory neuropathy type IV is characterized by normal fungiform papillae on the tongue, normal overflow tearing, normal tendon reflexes, no Jewish ancestry, and the absence of truncal sweating.

Progressive segmental anhidrosis with tonic pupils (Holmes-Adie syndrome with anhidrosis or Ross syndrome)

In 1958 Ross[97] first described the case of a 32-year-old man with a tonic pupil (Holmes-Adie syndrome), areflexia of the legs, and segmental progressive hypohidrosis. Since then, more than 10 similar cases have been reported in the English literature. Ross syndrome affects both men and women, and the age at onset ranges from 3 to 50 years.[98-100] Patients usually report heat intolerance (episodic palpitation and syncope during physical exercise in a hot environment), and their symptoms include the irregular segmental areas of anhidrosis on the trunk, arms, or legs. Examination of the pupils shows anisocoria, sluggish reaction to light, and abnormal constriction by 2.5% methacholine, symptoms that generally are ascribed to postganglionic denervation of the parasympathetic fibers that travel the third cranial nerve. An absence of deep tendon reflex in the arms and legs also is consistently seen. The mechanism of anhidrosis in these patients is unknown.

Progressive isolated segmental anhidrosis

A patient whose case was reported by Faden et al.[25] had anhidrosis without tonic pupils, sensory neuropathy, or areflexia. The anhidrotic areas remained responsive to intradermal cholinergic

agents for several months but became unresponsive 2 years after the onset of segmental anhidrosis. The authors therefore concluded that the anhidrosis in their patient was due to denervation of preganglionic sympathetic fibers. It remains unknown whether this patient had an incomplete form of Ross syndrome or a separate entity.

Generalized anhidroses of unknown causes

Fisher and Maibach[101] reported five cases of postural hypotension; two patients had generalized anhidrosis, and in a third the anhidrosis was localized. The authors suggested that the combination of postural hypotension and anhidrosis represents the basic features of the autonomic insufficiency syndrome. In contrast, eight cases reported by Low et al.[102] showed generalized anhidrosis with heat intolerance of 1 to 10 years' duration without orthostatic hypotension, for which the authors coined the term *chronic idiopathic anhidrosis.* Some of these patients, however, showed mild anisocoria, sluggish pupillary response to light and accommodation, and an abnormal pupillary response to cocaine and other agents, suggesting the involvement of mild postganglionic sympathetic failure. Five of them also showed electrophysiologic evidence of mild peripheral somatic sensory nerve involvement. One patient recovered from anhidrosis. The age at onset of symptoms ranged from 18 to 60 years, and histologic examination of the sweat glands appeared normal. Thus chronic idiopathic anhidrosis could be a forme fruste of acute panautonomic neuropathy.

The term *acquired generalized anhidrosis* was used for the condition of an 18-year-old man in whom generalized persistent anhidrosis developed after sunstroke at the age of 14 years.[103] A biopsy specimen showed the presence of numerous vacuoles in the secretory cells of the sweat glands. Unfortunately, multiple biopsies were not done to confirm the persistence of vacuolization. Postmiliarial hypohidrosis is known to cause longer-lasting hypohidrosis. So-called tropical anhidrotic asthenia with serious heat intolerance also may be a similar disorder.[104] Acquired generalized anhidrosis[104] and generalized anhidrosis after exposure to radiant heat[105] also may belong to the same spectrum as tropical anhidrotic asthenia. Sulzberger and Griffin[105] considered the possibility that anhidrosis in tropical anhidrotic asthenia is due not simply to poral occlusion but to central or peripheral neurologic damage and/or exhaustion of the eccrine secretory apparatus.[104] Anhidrosis of the legs is seen in 12% of patients with Guillain-Barré syndrome.[106] Patients with diabetic neuropathy are reported to have a reduced number of active sweat glands and low sweat rate per unit of skin area in proportion to the severity of neuropathy.[107] Extensive deposition of ceramide trihexoside in neurons of the autonomic and dorsal root ganglia and in the peripheral sensory and autonomic nerves, with resultant pandysautonomia and sensory neuropathy, can occur in Fabry's disease.[108-110] Thus gastrointestinal symptoms, limb paresthesias, dryness of the eyes and mouth, and hypohidrosis,[109,111] in addition to angiokeratoma corporis diffusum, renal disease, and cardiovascular disorders, may develop in some patients with Fabry's disease. The mechanism of hypohidrosis in Fabry's disease is not clear; however, uniform reduction in sweat rate has led Cable et al.[109] to suggest that the sweat gland itself may be involved rather than the autonomic nervous system. Kang et al.[111] observed the deposition of lamellar lipid granules in the ductal and secretory cells. Whether the lipid deposition itself directly destroyed the sweat glands, thereby causing hypohidrosis, or whether peripheral and central autonomic dysfunction was primarily involved remains to be studied. Generalized anhidrosis also is reported in association with Sjögren's syndrome[112] and in congenital ichthyosiform erythroderma.[113]

Localized hypohidrosis

Whenever sweat glands are damaged by surgery or trauma, scar formation, cutaneous neoplasms, irradiations, infection, inflammations of the skin, granulomatous lesions, sclerodermas, or vasculitis, localized hypohidrosis can occur. Because most of these are of no systemic consequence, they usually are ignored by the patient and the physician. Delivery of sweat to the skin surface may be impaired in a variety of dermatitides and papulosquamous diseases, presumably because of poral occlusion. However, it remains to be studied whether sweat secretion is stopped by the increased luminal pressure or whether sweat secretion continues and sweat simply migrates into the epidermis,

thereby aggravating the original inflammatory disease of the skin. It is not uncommon for patients with psoriasis or atopic dermatitis to report a burning sensation of the skin when they are placed in a hot sauna. This suggests that sweat secretion can occur under the papulosquamous lesions.

Skin blisters with underlying sweat gland necrosis have been reported in poisoning caused by barbiturates, methadone, diazepam, carbon monoxide, amitriptyline, and clorazepate.[114] It remains to be determined whether the blisters and the necrosis of the underlying sweat glands are due simply to pressure-induced ischemic changes of the skin or to direct damage of the sweat glands by the toxic doses of these agents.

Recently, Moss and Ince[115] observed the absence of sweating in the hypopigmented streaks and patches on the legs, arms, and scalp of 10 women with incontinentia pigmenti. A skin biopsy specimen revealed a lack of eccrine sweat glands and hair follicles in the anhidrotic hypopigmented lesions. The authors suggest that anhidrosis may be a common feature in the hypopigmented whirls and streaks of incontinentia pigmenti.

Sweat gland function in vitiligo has been poorly understood. Koga[116] observed that hypohidrosis occurs only in vitiligo that is dermatomally distributed, not in the nondermatomal type. He then advanced a hypothesis that the dermatomally distributed vitiligo may be caused by dysfunction of sympathetic fibers. The author postulates that the favorable response of dermatomally distributed vitiligo to oral nialamide (a monoamine oxidase inhibitor) is consistent with his hypothesis.

Anhidrosis of the face and neck has been reported in members of a family with follicular atrophoderma, basal cell carcinoma, and hypotrichosis, a rare X-linked dominantly inherited syndrome.[117]

In closing, we surmise that disorders of sweat secretion may be more prevalent than currently recognized. Continued search for abnormal sweating in various cutaneous and systemic disorders will help expand our knowledge of sweat gland function in health and disease. We hope that this review will serve as a source of recent references and will help stimulate the interest of dermatologists who, like ourselves, frequently encounter puzzling problems involving sweating disorders in their patients.

REFERENCES

1. Sato K. The physiology, pharmacology, biochemistry of the eccrine sweat glands. Rev Physiol Biochem Pharmacol 1977;79:51-131.
2. Momose T, Kunimoto M, Nishikawa J, Kasaka N, Ohtake T. N-isopropyl I-123 p-iodoamphetamine brain scans with single photon emission computed tomography: mental sweating and EEG abnormality. Radiat Med 1986;4(2):46-50.
3. Shih CJ, Wu JJ, Lin MT. Autonomic dysfunction in palmar hyperhidrosis. J Auton Nerv Syst 1983;8(1):33-43.
4. Holzle E, Alberti N. Long-term efficacy and side effects of tap water iontophoresis of palmoplantar hyperhidrosis—the usefulness of home therapy. Dermatologica 1987;175(3):126-35.
5. Pechman KJ, Bergfeld WF. Palmar-plantar hyperhidrosis occurring in a kindred with nail-patella syndrome. J Am Acad Dermatol 1980;3:627-32.
6. Aguirre-Negrete MG, Hernandez A, Ramirez-Soltero S, et al. Keratosis palmaris et plantaris with clinodactyly. Dermatologica 1981;162:300-3.
7. Demis JD, Dobson RL, McGuire J, eds. Clinical dermatology. Hagerstown, Md.: Harper & Row, 1980.
8. Cloward RB. Treatment of hyperhidrosis palmaris (sweaty hands). A familial disease in Japanese. Hawaii Med J 1957;16(4):381-9.
9. Cloward RB. Hyperhidrosis. J Neurosurg 1969;30:545-51.
10. Levit F. Simple device for the treatment of hyperhidrosis by iontophoresis. Arch Dermatol 1968;98:505-7.
11. Stolman LP. Treatment of excess sweating of the palms by iontophoresis. Arch Dermatol 1987;123:893-6.
12. Sloan JB, Soltani K. Iontophoresis in dermatology. J Am Acad Dermatol 1986;15:671-84.
13. Shelley W, Horvath P, Weidman F, Pillsbury DM. Experimental miliaria in man. I. Production of sweat retention anhidrosis and vesicles by means of iontophoresis. J Invest Dermatol 1948;11:275-91.
14. Timm D, Meletiou DS, Sato K. Mechanism of galvanic current-induced inhibition of palmer sweating in hyperhidrotic patients. Clin Res 1987;35:721A.
15. Welch E, Geary J. Current status of thoracic dorsal sympathectomy. J Vasc Surg 1984;1:202-12.
16. Golueke PJ, Garrett WV, Thompson JE, Talkington CM, Smith BL. Dorsal sympathectomy for hyperhidrosis—posterior paravertebral approach. Surgery 1988;103:568-72.
17. Chuang KS, Liou NH, Liu JC. New stereotactic technique for percutaneous thermocoagulation of upper thoracid ganglionectomy in cases of palmar hyperhidrosis. Neurosurgery 1988;22:600-4.
18. Malone PS, Cameron AE, Rennie JA. Endoscopic thoracic sympathectomy in the treatment of upper limb hyperhidrosis. Ann Rev Coll Surg Engl 1986;68(2):93-4.
19. Bretteville-Jensen G. Mossing N, Albrechtsen R. Surgical treatment of axillary hyperhidrosis in 123 patients. Acta Derm Venereol (Stockh) 1975;55:73-7.
20. Shelley WB, Hurley HJ. Studies on topical antiperspirant control of axillary hyperhidrosis. Acta Derm Venereol (Stockh) 1975;55:241-60.
21. Bandrup F, Larsen PO. Axillary hyperhidrosis: local

treatment with aluminum chloride hexahydrate 25% in absolute ethanol. Acta Derm Venereol (Stockh) 1978; 58:461-5.
22. Midtgaard K. A new device for the treatment of hyperhidrosis by iontophoresis. Br J Dermatol 1986; 114:485-8.
23. Shenaq SM, Spira M. Treatment of bilateral axillary hyperhidrosis by suction-assisted lipolysis technique. Ann Plast Surg 1987;19:548-51.
24. Greenhalgh RM, Rosengarten DS, Martin P. Role of sympathectomy for hyperhidrosis. Br Med J 1971;1: 332-4.
25. Faden AI, Chan P, Mendoza E. Progressive isolated segmental anhidrosis. Arch Neurol 1982;39:172-5.
26. Jane MJ, Freehafer AA, Hazel C, Lindan R, Joiner E. Autonomic dysreflexia. A cause of morbidity and mortality in orthopedic patients with spinal cord injury. Clin Orthop 1982;169:151-4.
27. Kewalramani LS. Autonomic dysreflexia in traumatic myelopathy. Am J Phys Med 1980;59:1-21.
28. Tashjian EA, Richter KJ. The value of propoxyphene hydrochloride (Darvon) for the treatment of hyperhidrosis in the spinal cord injured patient: an anecdotal experience and case reports. Paraplegia 1985;23:349-53.
29. Khurana RK. Orthostatic hypotension-induced autonomic dysreflexia. Neurology 1987;37:1221-4.
30. Steeten DHP, Kerr LP, Kerr CB, Prior JC. Hyperbradykininism: a new orthostatic syndrome. Lancet 1972; 2:1048-53.
31. Ottomo M, Heimburger RF. Alternating Horner's syndrome and hyperhidrosis due to dural adhesions following cervical spinal cord injury. J Neurosurg 1980;53:97-100.
32. Stanworth PA. The significance of hyperhidrosis in patients with post-traumatic syringomyelia. Paraplegia 1982;20:282-7.
33. Axelrod FB, Pearson J. Congenital sensory neuropathies. Diagnostic distinction from familial dysautonomia. Am J Dis Child 1984;138:947-54.
34. Green M, Behrendt H. Sweat gland reactivity to local thermal stimulation in dysautonomia. Am J Dis Child 1976;130:816-8.
35. Lisker R, Garcia-Ramos G, de la Rosa-Laris C, Diaz-Mitoma F. Peripheral motor neuropathy associated with autonomic dysfunction in two sisters: new hereditary syndrome? Am J Med Genet 1981;9:255-9.
36. Hines EA, Bannick EG. Intermittent hypothermia with disabling hyperhidrosis: report of a case with successful treatment. Mayo Clin Proc 1935;9:705-8.
37. LeWitt PA, Newman RP, Greenberg HS, Rocher LL, Calne DB, Ehrenkranz JRL. Episodic hyperhidrosis, hypothermia, and agenesis of corpus callosum. Neurology 1983;33:1122-9.
38. LeWitt PA. Hyperhidrosis and hypothermia responsive to oxybutynin. Neurology 1988;38:506-7.
39. Sandel ME, Abram PL, Horn LJ. Hypertension after brain injury: case report. Arch Phys Med Rehabil 1986; 67:469-72.
40. Cunliffe WJ, Johnson CE, Burton JL. Generalized hyperhidrosis following epilepsy. Br J Dermatol 1971; 85:186-8.
41. Eedy DJ, Corbett JR. Olfactory facial hyperhidrosis responding to amitriptylene. Clin Exp Dermatol 1987; 12:298-9.
42. Cunliffe WC, Johnson CE, Williamson DW. Localized unilateral hyperhidrosis—a clinical and laboratory study. Br J Dermatol 1972;86:374-8.
43. Fernandez G, Armijo M. Unilateral facial circumscribed hyperhidrosis. Acta Derm Venereol (Stockh) 1985;65:445-7.
44. Chan P, Kao GF, Pierson DL, Rodman OG. Episodic hyperhidrosis on the dorsum of hands. J Am Acad Dermatol 1985;12:937-42.
45. Van De Kerkhof PCM, Den Arend JAJC, Bousema MT, Stolz E. Localized unilateral hyperhidrosis. Br J Dermatol 1987;117:779-82.
46. Kuritzky A, Hering R, Goldhammer G, Becher M. Clonidine treatment in paroxysmal localized hyperhidrosis. Arch Neurol 1984;41:1210-1.
47. Pesonen K, Viinikka L, Koskimies A, Banks AR, Nicholson M, Perheentupa J. Size heterogeneity of epidermal growth factor in human body fluids. Life Sci 1987;40(26):2489-94.
48. Pancoast HK. Superior pulmonary sulcus tumor. JAMA 1932;99:1391-6.
49. McCoy BP. Apical pulmonary adenocarcinoma with contralateral hyperhidrosis. Arch Dermatol 1981; 117:659-61.
50. McEvoy M, Ryan E, Neal G, Prichard J. Unilateral hyperhidrosis—an unusual presentation of bronchial carcinoma. Ir J Med Sci 1982;151(2):51-2.
51. Pleet DL, Mandel S, Neilan B. Paroxysmal unilateral hyperhidrosis and malignant mesothelioma [Letter]. Arch Neurol 1983;40:256.
52. Allen JA, Lowe DC, Roddie IC, Wallace WFM. Studies on sweating in clinical and experimental thyrotoxicosis. Clin Sci Mol Med 1973;45:765-73.
53. Turkka JT, Myllylä VV. Sweating dysfunction in Parkinson's study. Eur Neurol 1987;26:1-7.
54. Appenzeller O, Gross JE. Autonomic deficits in Parkinson's syndrome. Arch Neurol 1971;24:50-7.
55. Aminoff MJ, Wilcox CS. Assessment of autonomic function in patients with a parkinsonian syndrome. Br Med J 1971;4:80-4.
56. Bravo EL, Gifford RW. Pheochromocytoma: diagnosis, localization and management. N Engl J Med 1984; 311:1298-303.
57. Allen JA, Armstrong JE, Roddie IC. Sweat responses of a hyperhidrotic subject. Br J Dermatol 1974;90:277-81.
58. Kenney MJ, Owen MD, Wall PT, Gisolfi CV. Characterization and quantitation of sweating in a systemic hyperhidrotic patient. Clin Exp Dermatol 1986;11:543-52.
59. Sohar E, Udassin R, Shoenfeld Y, Magazanik A. Cold-induced profuse sweating on back and chest. A new entity? Lancet 1978;2:1073-4.
60. Heckerling PS, Bartow TJ. Paradoxical diaphoresis in cyclobenzaprine poisoning [Letter]. Ann Intern Med 1987;101:881.
61. Cohen JB, Wilcox C. A comparison of fluoxipine, imipramine, and placebo in patients with major depressive disorder. J Clin Psychiatry 1985;46(3):26-31.
62. Tschernjawski J. Komplizierte Schweissdrüsennaevi mit Hyperfunktion derselben. Arch Dermatol Syph 1931; 162:762-70.
63. Cooke SAR. Misleading features in the clinical diagnosis of the peripheral glomus tumour. Br J Surg 1971; 58:602-6.

64. Kanitakis J, Roger H, Soubrier M, Dubost J-J, Chouvet B, Souteyrand P. Cutaneous angiomas in POEMS syndrome. Arch Dermatol 1988;124:695-8.
65. Sirinavin C, Buist NRM, Mokkhaves P. Digital clubbing, hyperhidrosis, acroosteolysis and osteoporosis. A case resembling pachydermoperiostosis. Clin Genet 1982;22:83-9.
66. McGibbon BM, Patetta FX. Further concepts in gustatory sweating. Plast Reconstr Surg 1972;49:639-42.
67. Friedman JH. Hemifacial gustatory sweating due to Pancoast's tumor. Am J Med 1987;82:1269-71.
68. Kux M. Thoracic endoscopic sympathectomy in palmar and axillary hyperhidrosis. Arch Surg 1978;113:264-6.
69. Kurchin A, Adar R, Zweig A, Mozes M. Gustatory phenomena after upper dorsal sympathectomy. Arch Neurol 1977;34:619-23.
70. Stuart DD. Diabetic gustatory sweating. Ann Intern Med 1978;89:223-4.
71. Drummond PD, Boyce GM, Lance JW. Postherpetic gustatory flushing and sweating. Ann Neurol 1987; 21:559-63.
72. Kornblut AD, Westphal P, Miehlke A. A reevaluation of the Frey's syndrome following parotid surgery. Arch Otolaryngol 1977;103:258-61.
73. Myers EN, Conley J. Gustatory sweating after radical neck dissection. Arch Otolaryngol 1970;91:534-42.
74. Gordon AB, Fiddian RV. Frey's syndrome after parotid surgery. Am J Surg 1976;132:54-8.
75. Harper KH, Spielvogel RL. Delayed onset of Frey's syndrome following trauma. J Assoc Milit Dermatol 1983;9(2):32-4.
76. Thomas RL. Tympanic neurectomy and chorda tympani section. Aust NZ J Surg 1980;50:352-5.
77. Bednarek J, Reid W, Matsumoto T. Frey's syndrome. Am J Surg 1976;1331:592-4.
78. Sessions RB, Roark DT, Alford BR. Frey's syndrome—a technical remedy. Ann Otol 1976;85:734-9.
79. Baddour HM, Ripley JF, Cortez EA, McAear JT, Steed DL, Tilson HB. Treatment of Frey's syndrome by an interpositional fascial graft: report of a case. J Oral Surg 1980;38:778-81.
80. Bronshvag MM. Spectrum of gustatory sweating, with especial reference to its presence in diabetics with autonomic neuropathy. Am J Clin Nutr 1978;31: 307-9.
81. Janka HU, Standl E, Mehnert H. Clonidine effect on diabetic gustatory sweating [Letter]. Ann Intern Med 1979;91:130.
82. Van Weerden TW, Houtman WA, Schweitzer NMJ, Minderhout JM. Lacrimal sweating in a patient with Reader's syndrome. Clin Neurol Neurosurg 1979; 81:119-21.
83. Becker RC, Alpert JS. Nocturnal diaphoresis in Prinzmetal angina [Letter]. Ann Intern Med 1987;107:121.
84. Tkach JR. Indomethacin treatment of generalized hyperhidrosis [Letter]. J Am Acad Dermatol 1982; 6:545.
85. Clarke A, Phillips DIM, Brown R, Harper PS. Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. Arch Dis Child 1987;62:989-96.
86. Clarke A. Hypohidrotic ectodermal dysplasia. J Med Genet 1987;24:659-63.
87. Freire-Maia N, Pinheiro M. Ectodermal dysplasia: a clinical and genetic study. New York: Alan R. Liss, 1984.
88. Lambert WC, Bilinski DL. Diagnostic pitfalls in anhidrotic ectodermal dysplasia: indications for palmar skin biopsy. Cutis 1983;31:182-7.
89. Arnold ML, Rauskolb R, Anton-Lamprecht I, Schinzel A, Schmid W. Prenatal diagnosis of anhidrotic ectodermal dysplasia. Prenat Diagn 1984;4:85-98.
90. Solomon LM, Keuer EJ. The ectodermal dysplasia. 1980; 116:1296-9.
91. Passarge E, Fries E. Autosomal recessive hypohidrotic ectodermal dysplasia with subclinical manifestation in the heterozygote. Birth Defects 1977;13(3C):95-100.
92. Beahrs JO, Lillington GA, Rosan RC, Russin L, Lindgren JA, Rowley PT. Anhidrotic ectodermal dysplasia: predisposition to bronchial disease. Ann Intern Med 1971;74:92-6.
93. Brengelmann GL, Freund PR, Rowell LB, Olerud JE, Kraning KK. Absence of active cutaneous vasodilation associated with congenital absence of sweat glands in human. Am J Phyiol 1981;240:H571-5.
94. Itoh Y, Yagishita S, Nakajima S, Nakano T. Congenital insensitivity to pain with anhidrosis: morphological and morphometrical studies on the skin and peripheral nerves. Neuropediatrics 1986;17:103-10.
95. Ishii N, Kawaguchi H, Miyake K, Nakajima H. Congenital sensory neuropathy with anhidrosis. Arch Dermatol 1988;124:564-6.
96. Vassella F, Emrich HM, Kraus-Ruppert R, Aufdermaur F, Tönz O. Congenital sensory neuropathy with anhidrosis. Arch Dis Child 1968;43:124-30.
97. Ross AT. Progressive selective sudomotor degeneration. Neurology 1958;8:809-17.
98. Esterly NB, Cantolino S, Alter BP, Brusilow SW. Pupillotonia, hyporeflexia, and segmental hypohidrosis: autonomic dysfunction in a child. J Pediatr 1968;73: 852-9.
99. Spector RH, Backman DL. Bilateral Adie's tonic pupil with anhidrosis and hyperthermia. Arch Neurol 1984;41:342-343.
100. Heath PD, Moss C, Cartlidge NEF. Ross syndrome and skin changes. Neurology 1982;32:1041-2.
101. Fisher DA, Maibach HI. Postural hypotension and anhidrosis. The autonomic insufficiency syndrome. Arch Dermatol 1970;102:527-31.
102. Low PA, Fealey RD, Sheps SG, Su WPD, Trautmann JC, Kuntz NL. Chronic idiopathic anhidrosis. Ann Neurol 1985;18:344-8.
103. Tsuji T, Yamamoto T. Acquired generalized anhidrosis. Arch Dermatol 1976;112:1310-4.
104. Sulzburger MB, Griffin TB. Induced miliaria, postmiliarial hypohidrosis, and some potential sequelae. Arch Dermatol 1969;99:145-51.
105. DaCosta JL, Tan KK. Generalized anhidrosis following exposure to radiant heat. Br J Dermatol 1966;78:312-21.
106. Singh NK, Jaiswai AK, Misra S, Srivastava PK. Assessment of autonomic dysfunction in Guillain-Barré syndrome and its prognostic implications. Acta Neurol Scand 1987;75:101-5.
107. Kennedy WR, Sakuta M, Sutherland D, Goetz FC. Quantitation of the sweating deficiency in diabetes mellitus. Ann Neurol 1984;15:482-8.
108. Rahman AN, Lindenberg R. The neuropathology of hereditary dystopic lipidosis. Arch Neurol 1963;9:373-85.
109. Cable WJL, Kolodny EH, Adams RD. Fabry disease:

impaired autonomic function. Neurology 1982;32:498-502.
110. Sima AFF, Robertson DM. Involvement of peripheral nerves and muscle in Fabry's disease: histologic, ultrastructural, and morphometric studies. Arch Neurol 1978;35:291-301.
111. Kang WH, Chun SI, Lee S. Generalized anhidrosis associated with Fabry's disease. J Am Acad Dermatol 1987;17:883-7.
112. Mitchell J, Greenspan J, Daniel T, Whitcher JP, Maibach HI. Anhidrosis (hypohidrosis) in Sjögren's syndrome. J Am Acad Dermatol 1987;16:233-5.
113. Salamon T, Budai V, Lazovic O, Macanocic K, Volic N. Klinische und therapeutische Kurzberichte. Erythrodermia ichthyosiformis congenita mit Hypotrichose, Anhidrose, Taubstummheit unt verminderter Ausscheidung einiger Aminosäuren in Harn. Hautarzt 1974;25:448-53.
114. Herschthal D, Robinson M. Blisters of the skin in coma induced by amitriptyline and clorazepate. Report of a case with underlying sweat gland necrosis. Arch Dermatol 1979;115:499.
115. Moss C, Ince P. Anhidrotic and achromians lesions in incontinentia pigmenti. Br J Dermatol 1987;116:839-49.
116. Koga M. Vitiligo: a new classification and therapy. Br J Dermatol 1987;97:255-61.
117. Viksnins P, Berlin A. Follicular atrophoderma and basal cell carcinomas. Arch Dermatol 1977;113:948-51.