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STUDIES ON TOPICAL ANTIPERSPIRANT CONTROL OF AXILLARY HYPERHIDROSIS

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Abstract. Axillary hyperhidrosis is reviewed from the standpoint of anatomical factors, physiological mechanisms and the history of methods of control. Anhydrous aluminum chloride and anhydrous zirconium tetrachloride are shown to be superior topical agents for partial control of axillary sweating when applied as a powder or in anhydrous nonreactive vehicles. Complete anhidrosis as demonstrated by sustained garment armpit dryness could be achieved in hyperhidrotics within 48 hours by the following trinary antiperspirant system: (1) a saturated solution of aluminum chloride hexahydrate or zirconyl chloride in absolute ethanol or isopropyl alcohol, (2) application to the dry axilla at times of sleep or other prolonged non-sweating period, (3) water vapor occlusion of area for 6 to 8 hours by means of Saran wrap®. The hypothesis is presented that metallic antiperspirants act by reflux entrance into the terminal intraepidermal eccrine duct, slowly combining with the intraductal keratin, to produce a fibrillar contraction (super contraction) of keratin and hence functional closure, not histologically evident. This altered keratin is shed weeks later, with the consequent return of ductal patency and sweating.

Key words: Antiperspirants; Hyperhidrosis; Sweating; Aluminum chloride

Despite the avalanche of topical antiperspirants which has descended upon the consumer, and despite the implications of the advertising claims, there is not a single topical agent available today which eliminates axillary sweating in the hyperhidrotic individual (39). Our awareness of this lack of an effective axillary antiperspirant formulation led us to this present study. Early on, we recognized that the problem was somehow uniquely related to the axilla and to the presence of hyperhidrosis (125). This seemed apparent since a variety of topical antiperspirants can produce complete anhidrosis when applied, for example, to the normhidrotic forearm rather than to the hyperhidrotic axilla (105). Accordingly, our survey and experimental studies are specifically focussed on the effect of topical agents on the strangely recalcitrant axillary sweating of man. Data on the control of sweating elsewhere, as well as animal and in vitro studies, have been excluded. In essence, we wish (1) to review the problem of axillary sweating and current knowledge of topical methods for its control, (2) to record our experimental observations on new anhydrous, water-activated antiperspirants, and finally (3) to present a new trinary antiperspirant system with effectively stops sweating in the hyperhidrotic axillae.

I. The Nature of Axillary Sweating and Hyperhidrosis

Although the axilla is virtually an apocrine organ (62), the profuse flow of sweat we term hyperhidrosis is the result of intense activity of the eccrine rather than the apocrine sweat glands in this area. Numbering about 25 000 in each axillary vault, these eccrine glands can secrete large quantities of sweat. In the hyperhidrotic, each armpit may produce upwards of 12 grams per hour (95). It is this heavy local outpouring which is so injurious to the affected individual's composure and clothes.

The responsible gland itself is a highly specialized yet grossly inapparent tubular derivative of the epidermis (94, 142), making its debut in the fifth fetal month. The business end of the gland is a blind secretory tube coiled deep in a dermal bed of large apocrine glands. The eccrine secretory coil ensheathed by a basket weave of contractile myoepithelial cells exhibits two morphologically unique cells (66). One is the clear cell, resting on the myoepithelium and exhibiting numerous mitochondria, stainable glycogen and a fine network of canalicular passageways to the lumen. This is the cell with the

Table I. *Compounds used as topical antiperspirants (4, 6, 30, 38, 54, 58, 75, 76, 98, 107, 139, 154, 158, 164)*

I. *Metallic*

Aluminum
- acetate
- acetotartrate
- alaninate
- allantoinates
- alcoholates
- aminoacetate
- argininate
- borate
- calcium chloride
- chloride
- chloroalcoholate
- chlorhydroxide complex
- chlorhydroxy allantoinate
- chlorhydroxide borate
- chlorhydroxy complexes
  - with propylene glycol
  - with lactate
- citrate
- dichloraminoacetate
- diethylmalate
- diketones
- ethylate
- formate
- gluconate
- glutamate
- glycinate
- hydroxide
- hydroxysulfonate
- lactate
- lysinate
- methionate
- nitrate
- palmitate
- phenolsulfonate
- phosphate
- potassium, ammonium sulfate
- sodium picrate
- sodium lactate
- sulfamate
- sulfate
- sulfoacetate
- sulfobenzoate
- sulfocarbolate
- trisulfonate
- and many complex organic derivatives

Zirconium
- chloride
- citrate
- hydroxychloride
- methionate
- nitrate
- oxychloride
- sodium gluconate
- sodium lactate
- tartrate
- trichloraluminate

Zinc
- chloride
- methionate
- octa decenyl succinate
- oleate
- phenolsulfonate
- sulfamate
- sulfate

Miscellaneous salts of
- beryllium
- bismuth
- cerium
- chromium
- copper
- hafnium
- iron
- lanthanum
- lead
- magnesium
- mercury
- nickel
- neodymium
- praeseodymium
- samarium
- silver
- tin
- titanium

II. *Organic*

Anticholinergic, e.g.
- atropine methyl nitrate sulfate
- homatropine methyl bromide
- scopolamine hydrobromide and esters

Acids
- boric
- salicylic
- malonic
- sulfosalicylic
- tannic
- trichloracetic

Aldehydes
- formaldehyde
- glutaraldehyde

Quaternary ammonium compounds
- benzalkonium (Zephiran®)

sodium pump responsible for the isotonic transfer of electrolytes and fluids from the periglandular space to the lumen (31). The other secretory cell is the dark cell, a pyramidal cell inverted, as it were, over the clear cell, and thus having its base line on the lumen. This is the cell responsible for secretion of mucopolysaccharides, rather than the fluid component of sweat. In turn, the external myoepithelium provides the contractile element responsible for the pulsatile delivery of the final product (97).

The entire secretory coil is surrounded by cholinesterase-rich autonomic nerve endings under both hypothalamic and cortical controls. All this reflects the dual role of the axillary eccrine sweat gland, viz. evaporative cooling and, more importantly, an

atavistic protective volatilization of the odorants of apocrine sweat in times of threat. Notable in this regard is the fact that in pronounced hyperhidrosis, there is no axillary odor, the bacteria–apocrine synergistic system being flushed away (62). Also, interestingly, the other focal areas of stress eccrine sweating, i.e. the palms and soles, serve the function of increasing friction providing a better grip "for fight or flight" (29). The glands thus will secrete in response to local cholinergic drugs and to a lesser extent to adrenergic compounds (32). Parenthetically, Soto has brilliantly shown that the responses of the single isolated gland in vitro are identical to both mecholyl and epinephrine (120).

Physiologically, the same eccrine gland of the axilla will also respond to either thermal or emotional stress, or both (80). However, the axillary response to emotional stress seems conditioned by hormonal factors common to the development of the apocrine gland, since neither emotional hyperhidrosis nor apocrine sweating is ordinarily experienced before puberty (74). Pharmacologic testing with intradermal mecholyl demonstrates that the axillary glands are often a hundred fold more sensitive than the adjacent eccrine glands on the chest (110). Not only are the axillary areas hyperresponsive to pharmacologic stimulation in the hyperhidrotics, but their eccrine glands over the entire body are more responsive to mental stress than those of normal individuals (3). Significantly, this is limited to mental stress and is not seen with thermal stress. Yet enzymatic, histologic and neural studies still fail to reveal an identifiable difference in the glands of the patient with hyperhidrosis and the normhidrotic control population (63).

The several centimeters of glomerular coil of the gland lead into a thin undulating excretory duct. This conduit of about 30 μm in diameter has a doublet of cuboidal cell lining which reabsorbs part of the essential sodium, leaving the final sweat hypotonic to plasma (19). It is this ductal lining which during the adaptive acclimatization of repeated sweating becomes more efficient in producing just the water essential for evaporative cooling, without the critical loss of large amounts of electrolytes.

Finally the duct passes into the epidermis where, as an acrosyringium, it spirals four to six times in a right-handed coil patterning (21, 142). The duct is collapsed and without lumen (34), except during sweating or in the presence of occlusive sweat retention. It ends in an inapparent slit, in the stratum corneum (70, 117, 161). The orifice of the gland is nowhere to be seen in the surface topography. It does not stain distinctly with methylene blue (102). Even on electron scan micrography it is not evident except by chance in an area where stratum corneum cells have been removed (105). It is only the palms and soles that show the dramatic pit openings into the epidermal sweat duct (141). Despite its inapparent nature the intra-epidermal sweat duct is a distinctive structure, anatomically and chemically (85). It is without melanocytes and hence non-pigmented. It exhibits a special resistance to alkaline maceration. The most significant finding is the fact that the luminal cells lining this duct, as well as a surrounding sheath several cells in thickness, are keratinocytes which actively form keratin (57, 141). Thus, the upper end of the intra-epidermal sweat duct is keratin lined.

Although one can measure the sodium, potassium, lactate, urea, proteins, amino acids, the pH, or a host of trace chemicals in sweat, the measurement of concern in the hyperhidrotic is a quantitative one. How much sweat is being formed in response to a given mental, emotional, thermal or pharmacologic stimulus?

The simplest assessment is made on direct visual estimation or photographic representation (17, 91). The spontaneous appearance of gross visible droplets of sweat in the axilla is prima facie evidence of stress hyperhidrosis (127). Less direct but equally impressive and practical is the observance of wetting of the armpit of the clothing worn. Although measurements of the size of the wetted area cannot serve as an absolute, since the texture, thickness, and fit of the garment vary even as the ambient humidity, air flow and temperature, we have found them to be clinically significant observations in simultaneous paired comparison studies of the effect of antiperspirants. We have also found that direct application of a single sheet of Kleenex® to the extended axilla gives an immediate visual "wetness" estimate of the degree of sweating. In our experience it is superior to simply looking at the sweat droplets.

A second major approach to evaluation of sweating in the axilla is indirect in nature, for example by colorimetric contact print or surface replication techniques. In the colorimetric, such as in Minor's method (93), the sweat is visualized by the purple color it induces in starch powder directly patted on, or applied in castor oil (149) to skin first

painted with iodine. On dark skins, reading is facilitated by white background achieved by adding titanium dioxide to the starch oil (150). A variant is to visualize the sweat droplets in a starch paper firmly applied to the iodine painted skin (109). Indeed the iodine does not have to be painted on the skin but may be sublimed into the paper before (33) or after (101) the sweat imprint is made. Other colorimetric methods are based on color changes that are water induced in specific chemicals such as the dye quinizarin (53), ferric chloride (129), cobalt chloride (81, 115) or bromophenol blue (55, 143). In another test procedure, silver salts are rendered visible by the reaction with the sweat chlorides (35, 52, 130). A degree of quantitation can be afforded by densitometry readings of the color change (37). The newer indirect ways of quantitating sweat droplet formation rest on forming a silicone type replication of the skin surface. Should sweating occur during this procedure, the sweat droplets form apertures in the hydrophilic replication material which can then be counted and assayed (145, 159).

The third and most popular technique is a direct one, viz. weighing of tared Webril® pads or filter paper placed in close axillary apposition under a water-impermeable covering for a precise given period of minutes while the subject is exposed to definable thermal and/or emotional stress (16, 28, 41, 42, 68).

Finally, the most sophisticated, expensive, and complex techniques rest on measurements of the amount of water vapor which appears in a dry inert gas passed through a cup covering a known area of axillary skin. This is achieved by (i) weighing the cryo-condensate (7, 96) or (ii) determining the relative humidity by wet and dry bulb readings (88) or (iii) determining the moisture content electronically (1, 26, 146, 156), for example with a film (18) or plastic sensor (96, 113) or electrolytic sulfuric acid cell (23), or by (iv) measurements based on infra red gas analysis (13, 100, 152). A major defect in all of the available quantitative methods is that the emotional sweating response is assessed only for minutes. The need for continuous monitoring over many hours to record the cumulative sweating responses from repetitive emotional stimulation prompted us to use a new "garment wetness surface area" technique (Table II).

An ancillary means of detecting sweating, though not for quantitating it, is the determination of the resistivity or capacitance changes which herald eccrine sweating (2, 90, 96, 157). The drop in resistance associated with sweating is one of the parameters used in lie detector testing, and, although usually related to the palms, is equally valid in the axilla.

All of these measurements and observations have told us the following about axillary eccrine sweating and hyperhidrosis (63, 80, 110):

(1) Axillary sweating is intermittent, fluctuant, being responsive to emotional stress, as well as to thermal stimuli.

(2) It is usually absent when the patient is asleep or at rest at night or other times.

(3) The same gland will respond to both emotional or thermal stress but is more reactive to emotional stress than to thermal.

(4) Emotional responses are conditioned and potentiated by a warm environment, summer temperatures or hyperthermia. Actually a greater amount of sweat is secreted. The heightened response is not simply due to a decrease in evaporation.

(5) Axillary hyperhidrosis is familial, not present in childhood, rare in the aged, results from locally hyperresponsive eccrine sweat glands in the young adult, both male and female.

(6) Often there is a constant asymmetry in axillary sweat rates, the right side being more active than the left.

(7) Control is achieved with difficulty, as detailed in the following section.

II. Methods of Control of Axillary Hyperhidrosis

An awareness of the physiology of the sweat gland makes one realize that there are many mechanisms which may be interrupted or altered to achieve control of hyperhidrosis. The hyperfunctioning gland is not autonomous, but rather is responding to sympathetic nerve discharges which in turn result from cortical responses to stress. From the clinical standpoint the major stress stimulus is emotional (12), and it is here that much can be done by the patient either to avoid occupational or social circumstances which are anxiety provoking or to consciously minimize his response. The patient must be a student of the art of relaxation, of how to be less tense, of how to shrug the shoulder rather than clench the fist. Rest and relaxation often are the best prescriptions for hyperhidrosis. For some,

relief comes only with the passage of time, and the gradual acceptance of the world as it is. Interestingly, it is possible to reduce non-thermal sweating by employing a painful shock conditioning system (81). We can say that under these experimental conditions the subjects "learned" to decrease their sweat rate markedly.

From the practical medical standpoint, there are two distinct classes of pharmacologic aid. The first are the tranquillizers which affect higher centers, and the second the anticholinergic agents which block adeno-neural transmission. It is possible with Valium (25) or a variety of its congeners to induce in a patient a degree of indifference to both internal and external emotional stimuli. Under such a setting, autonomic discharge and hence the hyperhidrosis ceases. The goal is to find a dosage which shuts down the patient's hyperhidrosis but not his effectiveness. The other group consists of those drugs which block autonomic transmission. Here the anticholinergic agents have long been popular, beginning with tincture of belladonna and extending to Probanthine® (propantheline bromide—Searle & Co. G.D., Chicago, Ill.) (24, 25, 44, 112). The oral ganglionic blocking agent hexamethonium has also been shown to be effective (132). But with all these drugs, there is no specificity, and the concomitant dry mouth, blurred vision, urinary retention and tachycardia can be far more disconcerting than the hyperhidrosis.

From the surgical side, more can be done (56, 86). Although sympathectomy would appear to be an ideal method of control, in the case of the axillary hyperhidrosis, the results are not consistently reliable (49), probably because of the variability of the anatomic pathways. Furthermore, it is a procedure not without risk, two deaths having been reported (151). Far more satisfactory is the local excision of the gland-bearing axillary skin. As we first demonstrated in 1963, hyperresponsive glands usually occur in well circumscribed control area of the axilla, the major site of sweat production can be mapped and then excised with permanent ablation of the end organ in the problem of hyperhidrosis (64). Such a procedure may range from such a simple dermatologic office excision, to a more extensive removal with undercutting (43, 63, 95). In a few patients plastic surgical removal of the entire skin of the axillary vault (14, 131) may be necessary to produce a dry armpit. Radiotheraphy has not proven satisfactory, since a dosage which eliminates sweating, produces radiodermatitis, with its train of misfortunes (11, 22). Finally, immunosympathectomy is still so new as to await even animal studies (134).

Although medical and surgical procedures provide their measure of relief, it is to the topical remedies that most patients with hyperhidrosis turn. Here one has the promise of a treatment which is local, safe and inexpensive. It is not a treatment requiring medical supervision, prescriptions or surgical intervention. As such it has spawned an entire industry which in the U.S. alone sells several hundred million dollars worth of axillary antiperspirant-deodorants each year.

The modern story of topical antiperspirants for the axilla all began with Stillians' observation in 1916 that 25% aluminum chloride hexahydrate in distilled water dabbed gently on the armpit every second or third day will ameliorate excessive sweating (136). Prior to that a variety of astringent lotions containing tannin, zinc sulfate or alum (ammonium or potassium aluminum sulfate) were used with indifferent results (135). Stillians found that his formulation usually gave relief after three applications, subsequent use being limited as needed or once a week. He cautioned that the solution should dry completely before clothing was allowed to touch the skin. He found in twenty patients that the preparation was not completely bland, excessive use producing sharp itching or stinging, even dermatitis, but that this subsided spontaneously. In any event the delight of the patients in being able to discard dress shields was evident.

The subsequent research and development in the field has been truly phenomenal, with a vast literature spreading throughout medical reviews (58) and monographs (38, 107, 139), cosmetic and pharmacy texts and reports (4, 25, 47, 76, 77, 99, 154, 158, 164), foreign articles (54), the patent files (30), and still much remains as hidden data within the companies themselves. To date, the most magnificent detailed comprehensive review of the subject of antiperspirants is that by Fiedler (38). It is adorned with 411 references. From all these sources we will try to historically highlight the major threads of research and thinking which have appeared.

It is fascinating that today, despite fifty-eight more years of study, Stillians' formulation of 1916 still remains the most effective practical antiperspirant in use. It is the benchmark antiperspirant against which new contenders are surveyed. It is

not toxic and it is not allergenic! Nonetheless, it enjoys only a limited sale today because (a) it is irritating to the skin of some users, (b) its high acidity is damaging to clothing, (c) it is awkward to apply, and furthermore (d) it reduces sweating by only about 50%. Recognition of these four drawbacks came early and a review of the literature gives a panorama of innumerable efforts to improve on the Stillians' method.

The first developmental change came with the discovery in the 1940s that a less acidic complex salt of aluminum, viz. aluminum chlorhydroxide, could be substituted for the aluminum chloride. This reduced irritation to the skin and markedly lessened the damage to clothing. Unfortunately it also reduced the antiperspirant effect, but this sacrifice was accepted by industry since the aluminum ion was so remarkably active as a deodorant that the new product suffered no loss in deodorant power (125). The public to a large degree was more interested in deodorant than antiperspirant activity, but this dual role of aluminum early led to advertising claims which blurred the distinction of the two disparate effects. The words deodorant and antiperspirant became loosely interchangeable. Meanwhile the hyperhidrotic individual's lot was not improved by the widespread adoption of a less effective antiperspirant.

Literally dozens of other aluminum inorganic and organic salts have been tried (30), many have been patented and a few enjoyed a short popularity. Among the latter are aluminum phenolsulfonate (153), aluminum sulfate, sodium aluminum lactate, aluminum formate (99), and currently an aluminum chlorhydroxy complex with propylene glycol (Rehydrol®) used in the anhydrous alcoholic aerosol formulations (6). None is as irritating or as effective as the original aluminum chloride.

For every new aluminum salt tried there must have been a hundred new vehicles proposed. The formularies down through the years are literally cook books filled with recipes for compact powders, liquids, colognes, emulsions and creams (6). Fragrance, color body, stability, hexachlorophene, surfactants, humectants and buffers were added with the consummate art of professional compounding, but always without any increase in effectiveness. It became evident that the aluminum salts could show optimal antiperspirant activity only when they were presented to the skin in ionic form (76). The highly complex organic vehicles proved to be a chemical hindrance to the reaction of the aluminum on the skin. Only the addition of the new penetrant vehicle dimethyl sulfoxide, DMSO, in a 50% aqueous solution was found to enhance the action of aluminum chloride (78). But it cannot be used even under prescription in the United States, for it is still an experimental drug. Stillians' aqueous formulation remained the best practical antiperspirant, but in the market place the buffered aluminum chlorhydroxide in a cosmetic cream prevailed since in general it neither irritated the skin nor damaged clothing. And it was an ideal deodorant, even if a lesser antiperspirant.

Industry addressed itself also to the problem of application. The dabbing of an acidic dripping solution on the skin gave way to the manual atomizer mist spray of the 'thirties. Cotton cloth pads impregnated with the antiperspirant solution provided an alternative to the cream. Later an ingenious, finely fitted, plastic ball top applicator allowed the consumer to roll-on a tailored emulsion formula of the aluminum chlorhydroxy salt. In the physician's office, iontophoresis has been employed, but to a very limited extent (7, 65). An equally remarkable method of application was the antiperspirant stick in which the active compound was incorporated into a soap gel or wax formulation which could be neatly rubbed over the axilla. The ultimate in simplicity was to come with the development of the aerosol dispenser for the antiperspirant. By using a complex of the aluminum chlorhydroxide with propylene glycol, an antiperspirant was formulated which could be dissolved in alcohol, did not clog valves of the aerosol dispenser, and could be prepared with the usual propellants. This has proven to be the most popular method of application, despite the obvious problems of inhalation and potential eye hazards. Still again the product development moved away from antiperspirant efficacy toward general consumer acceptance. The hyperhidrotic is in the minority. The products sold largely because they remained excellent deodorants. Elimination of the odor-producing bacteria population in the axillae is far easier than elimination of sweating.

Investigators have not limited their efforts to mere study of aluminum salts, vehicles and modes of application. An unbelievable array of related and unrelated compounds have been assessed for possible antiperspirant activity (Table I). The successes are best scanned as groups.

It has been established that virtually any metallic

salt may be expected to show a topical antiperspirant effect. Many can be eliminated because of allergenicity—such as nickel, chromium, and beryllium. The lead salts known to inhibit sweating even before aluminum pose the problem of toxicity, as do the cadmium and mercury salts. Parenthetically it is significant that the Food and Drug Administration (FDA) regulations control the testing and approval of antiperspirant formulations as new drugs, since they affect a bodily function. Furthermore the active ingredients must be clearly printed on the label. In contrast, deodorants are classified as cosmetics—beyond the close scrutiny of such government review. However, both groups remain under the Federal Trade Commission (FTC) truth in advertising code. Iron and silver salts may produce tattoos. Other metallic salts such as gold, silver and the rare earths are beyond consumer pricing, for all require high concentrations, and do not act in trace amounts.

Salts such as acetate were unacceptable due to odor. Others proved undesirable due to their instability or reactivity. However, two metals of this group have been and continue to be employed successfully in currently used antiperspirants. These are zirconium and zinc. Sodium zirconium lactate in a stick preparation (126) was an effective antiperspirant but its use had to be discontinued when it was found to induce axillary granulomas on an immune basis. Subsequently zirconium has been used as the chlorhydroxide salt with success in other vehicles. Zinc has been most commonly used as the phenol sulfonate.

The acidic nature of these salts led to a study of acids themselves and a few seemed to have a minor antiperspirant effect. These include boric, salicylic, tannic, trichloracetic acid, and even malonic acid (133). None is used today. More success greeted the study of another group of highly reactive chemicals, viz. the aldehydes. Formaldehyde but not glutaraldehyde (72) has been shown to be effective in reducing axillary perspiration, whereas acetaldehyde is without effect and proprionaldehyde favors sweating (61). However, although formaldehyde is commonly used in Europe (133), it is far too powerful a sensitizer to have met favor in the United States. Glutaraldehyde, another contact allergen, also suffers the severe disadvantage of staining the skin of the axilla a dirty yellow brown (47). Endless combinations and permutations of metals, acids, aldehydes, pH, and vehicles brought the state of the art no closer to an antiperspirant (15, 47, 60, 61).

The final main avenue of study of topical antiperspirants was opened by us in 1951. At the time we demonstrated that the topical application of aqueous solutions of concentrated scopalamine hydrobromide to the forearm could produce virtually complete anhidrosis for over three weeks (124). The matter was further studied by others in depth (89), and it was found that when dilute aqueous solutions of scopolamine esters (0.05%), for example the butyrate, were applied to the axilla, sweating was reduced by 95% five hours later. Despite the great promise of this pharmacologic approach, no commercial preparation is available, due to the instability of the compounds (158) and because of the dangers of systemic effects resulting from percutaneous absorption. These and similar preparations (7, 36, 40, 51, 84, 137) are still used on an experimental basis in the United States.

To summarize, Stillians' 25% aluminum chloride in aqueous solution remains the best practical antiperspirant to date, but it still has four limitations. After six decades, what has been done to overcome these? (1) To overcome the irritancy, aluminum chloride has been replaced by a less acidic compound, aluminum chlorhydroxide, recognizing that this has been done by sacrificing some degree of efficacy. (2) To overcome clothing damage by aluminum chloride, some few advise applying the formula at night and washing carefully in the morning. Generally, however, the substitution of aluminum chlorhydroxide minimized deleterious effects on clothing, and the antiperspirant can be applied any time. (3) For ease of application the indirect techniques of a roll-on or aerosol spray have proven superior to direct finger application. (4) No advance has been made in efficacy. With the exception of the unstable experimental topical anticholinergics and the formulations with DMSO, none of the thousands of compounds and formulations tried have consistently surpassed even the limited anhidrotic effect of Stillians' original aluminum chloride preparation. The need for a truly effective topical antiperspirant remains and was the stimulus for the following study which was carried out by us over a seven year span.

Before turning to our personal experiences, it may be well to review what is known concerning the mechanism of anhidrosis as produced by aluminum chloride, its congeners, and other topical

anhidrotics. It is easiest to dismiss the anticholinergics. Absorbed through the apopilosebaceous apparatus, they enter the dermis to block the cholinergic impulses from the neural network which activates the eccrine glands. Sweat secretion is accordingly stopped. All this reflects a relative permeability of the axillary epidermal appendages to these compounds and a capacity to act in extremely low concentrations (89).

In regard to aluminum chloride, the mechanism is more obscure. Originally it was considered an astringent which simply closed the sweat pore. Certainly subsequent study has confirmed a superficial site of action. Aluminum is not found in the axillary dermis (8), but rather in the stratum corneum and intraluminally in the terminal duct as shown in animal studies (83). We further know that aluminum chloride is highly acidic—Stillians' aqueous solution of 25% strength has a pH of 2.0 (158). As such, it readily binds to be carboxyl groups of the stratum corneum (84). Yet histologic study has failed to reveal a solid anatomic basis for occlusion (104). Moreover, Scotch tape stripping off of the stratum corneum from an aluminum chloride anhidrotic site fails to restory sweating (45, 105) in the manner in which it can be done in a site rendered anhidrotic by glutaraldehyde (119). Yet these studies were done on the forearm. The only histologic observations made in the axilla were done with aluminum sulfate, a remarkably ineffective antiperspirant (47). They showed mainly a non-specific dermal inflammatory change (138). The fact that aluminum chloride acts only superficially, does not penetrate into the dermis, suggests that it produces anhidrosis by poral closure, with consequent asymptomatic sweat retention (123). Although it has been suggested that aluminum anhidrosis results from leakage of sweat through the duct wall in the presence of a patent pore (105), there is little to support this rather strange hypothesis.

The mechanism of anhidrosis production with zirconium, zinc and the other metallic salts is presumed similar to aluminum in view of their similar chemical properties. All are protein precipitants and bind to keratin. As to glutaraldehyde the obstructive change induced in the ductal site is more superficial inasmuch as Scotch tape strippings rapidly restore sweating capabilities to normal once the obstructive layer of corneum is pulled away. Our studies with anhidrosis due to non-specific epidermal injury such as induced by hydration or chemicals likewise suggest a superficial poral keratinous plugging which is shed as the corneum normally desquamates (123). Similarly, prolonged occlusion of skin by Saran wrap® or adhesive is followed by miliarial anhidrosis related to the enormous overgrowth of bacteria which occurs (46, 104, 140, 160).

Note should be made of fact that hydration of the palms and soles reduces sweating. Here the mechanism involves simple swelling of the remarkably thick stratum corneum found only at these sites. Indeed, the sweat pores normally so uniquely prominent in these areas become completely invisible when the skin is soaked in water for 90 minutes (118).

III. Experimental Studies on Water-Activated Antiperspirants

A major advantage of topical therapy is the gross localization of the treatment to the skin. This advantage is achieved daily in treating skin disease, and is the basis for the tremendous sale of "over the counter" antiperspirants. But in the case of a topical antiperspirant, might we not achieve even greater precision in localization if somehow the action could be limited to the 30 μm terminal sweat pores themselves? But how? The pore seems little different from the landscape of the surrounding stratum corneum other than for the presence of a potential, virtually hidden, spiral channel. And yet the pore is unique, for it is the "wet spot" of the skin surface. Might not a chemical, activated only by the water of sweat as it emerged from the pore, give us the ultimate in selective localization of therapy?

Amazingly the search for suitable water-activated compounds brought us right back to the two most effective metallic antiperspirants, aluminum chloride and zirconium chloride, but this time in their powerful non-hydrated, i.e. anhydrous, form. No one has ever used either compound in its highly reactive water-free state directly as an antiperspirant, although the anhydrous forms of both are well known powerful catalysts in the famed Friedel-Crafts reaction (10, 144). It should be made clear that, although both the cosmeticians and the chemists may refer to aluminum chloride, the cosmetician is speaking of the hexahydrate, and the chemist is referring with precision to anhydrous aluminum chloride. There is less confusion with zirconium, where the term zirconyl chloride refers to the

octahydrate and zirconium tetrachloride only to the anhydrous form. The individuals concerned with antiperspirants either are unaware of the anhydrous versions or view them as toxic, caustic, explosive catalytic compounds used only in industrial synthesis or the chemical research laboratory. Yet we became interested in them because one of their most striking properties is their capacity to react immediately and violently with water, forming the hydrated salts and nascent hydrochloric acid. Thus the reactions may be formulated:

$$2AlCl_3 + 3H_2O \rightarrow Al_2O_3 + 6HCl$$

$$ZRCl_4 + 9H_2O \rightarrow ZrOCl_2\ 8H_2O + 2HCl$$

The following experiments explored the possibility of using anhydrous aluminum and zirconium halides directly on the skin as agents which would give focal effects precisely limited to the wet spot of the sweat pore.

The application of anhydrous aluminum chloride power to the dry axilla produced little in the way of immediate observable change. However, once sweating was induced by mental arithmetic, tiny powdery explosive reactions could be seen and the exothermic reaction felt by the patient. A degree of anhidrosis could be induced, but it was recognized that surface application was not ideal. To induce poral closure the aluminum chloride should actually enter the pore. Accordingly the anhydrous aluminum chloride was dissolved in anhydrous ethyl ether. Slide tests revealed that in this vehicle the aluminum chloride retained its visible reactivity with water. Significant anhidrosis was achieved by its topical application in concentrations of 5, 10 and 15%. Using a starch iodine assay of the sweat response to mental arithmetic, each one of a group of 6 subjects showed a 4+ reduction in sweating in the axilla treated with 15% aluminum chloride in ethyl ether on each of the two days preceding the readings. An additional 6 men were similarly treated with anhydrous aluminum chloride power (particle size less than 74 μm as a 1% suspension), dispensed in an aerosol using dichlorotetrafluoroethane Freon 114 as a propellent. One man showed a 4+ reduction, 4 showed 3+ reduction, and one man who was hyperhidrotic showed no effect. All showed complete absence of axillary odor.

It was found that the preparations had to be applied to dry non-sweating skin or else the irritation and stinging was marked. Use of the anhydrous aluminum chloride in absolute ethyl alcohol was less effective. Acetone did not prove to be an adequate vehicle due to the resultant color changes and instability.

The anhydrous zirconium tetrachloride power is a very smooth, fine tan powder, and when simply rubbed into the dry axilla of 5 subjects produced a marked sweat reduction as seen by comparative starch-iodine readings 48 hours later. The reductions were rated as 4+, 4+, 3+, 2+, and 0. The absence of effect was again noted in one hyperhidrotic subject of the group. In 5 subjects, the antiperspirant activity of the zirconium tetrachloride powder was compared at 48 hours with a standard commercial aluminum chlorhydroxide and zirconium oxychloride roll-on antiperspirant preparation. The comparisons were made gravimetrically using a Webril cotton technique and a five minute mental and thermal stress. In each instance the zirconium tetrachloride produced a greater degree of reduction, viz., 38%, 16%, 44%, 51% and 38%, or an average of 37% greater reduction on the zirconium tetrachloride powder side. Zirconium tetrachloride powder proved to be superior to anhydrous aluminum chloride powder which did not have the fine, velvet feel, nor was the anhydrous aluminum chloride as consistently effective in reducing sweating. Dissolved in ethyl alcohol, zirconium tetrachloride was less effective than in acetone and both were unstable, with the preparations losing their antiperspirant action over a period of time. With freshly prepared 5% zirconium tetrachloride in acetone, 3 subjects showed at 48 hours starch iodine imprint reductions of 4+, 4− and 3+ respectively. Use of zirconium tetrachloride suspended in mineral oil or in silane was without effect.

The most consistent reductions in sweating were seen with the use of a 1% zirconium tetrachloride in a Freon 114 aerosol dispenser. Such a propellent system involved a dip tube of nylon, a special powder valve to minimize valve clogging, and the avoidance of trichloromonofluoromethane Freon 11® with which the zirconium tetrachloride is highly reactive. In 20 subjects, applications on 2 subsequent mornings to the dry axilla gave starch-iodine readings on the third day of 4+ reduction in 11 subjects (Fig. 1), 3+ reaction in 4 subjects and 0 reduction in 5 subjects. Every one of the 5 subjects who showed no effect was a hyperhidrotic individual. The opposite axilla in each of the 20 subjects was treated the same way with a standard commercial spray antiperspirant (Fig. 2).

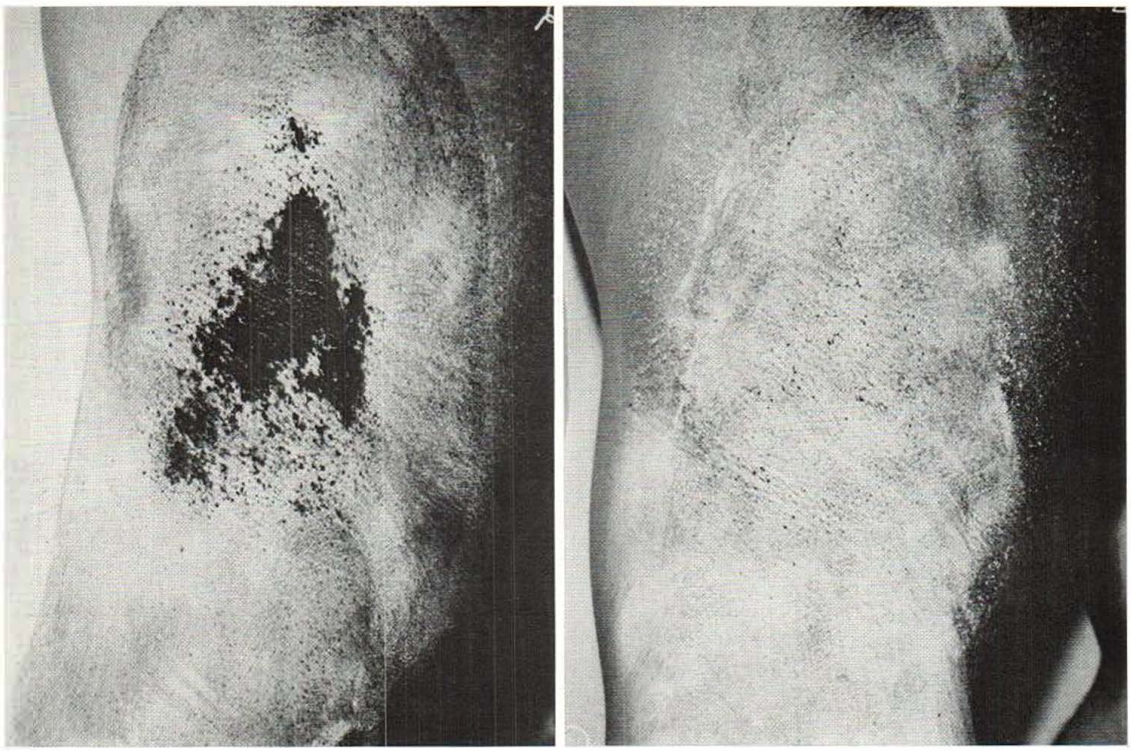

Fig. 1. Effect of anhydrous zirconium tetrachloride powder (1%) aerosol spray. On the left is the subject's shaved right axilla, showing the starch-iodine sweat response to mental and termal stress before treatment. To the right is the same axilla following similar stress 48 hours later, after two treatments with zirconium powder spray. The marked reduction in sweating is evident. Contrast with Fig. 2, showing simultaneous control in left axilla.

IV. Experimental Studies on Binary and Trinary Antiperspirant Systems

A. The binary system

The anhydrous aluminum and zirconium salts were remarkably effective as antiperspirants. Yet the fact that they failed to affect materially the gross sweat patterns of hyperhidrotic individuals, indicated the need for more study. The resistance of the axillary area to antiperspirants was tantalizing. One can regularly achieve a 100% reduction in sweating on the forearm or the back with 20% aluminum chloride hexahydrate aqueous solution applied under occlusion. But not in the axilla (104). Is the eccrine sweat unit anatomically different in the axilla? Is the pore too large to occlude? Is the keratinization cycle different? Does the apocrine sweat interfere? Or does one need simply a stronger antiperspirant system? We conducted the following pilot studies to see if using adjuvant procedures might accentuate the antiperspirant effect of aluminum chloride hexahydrate solutions, and thus provide the clinical antiperspirant effect sought by hyperhidrotic individuals. Some of the studies stemmed from the techniques of waterproofing (111), but in no instance could we achieve the critical high temperatures regularly employed in this type of textile processing. Evaluations were made by observing and recording the area of wetness in the armpit area of clothing during periods of normal daily emotional and thermal stress. Paired comparison data for each adjuvant procedure were collected on groups of 3 subjects, except for the study on iron chelation wherein 15 subjects participated. The following 7 adjunctive measures were studied each without producing any notable increase in the effectiveness of a 20% aluminum chloride hexahydrate aqueous antiperspirant solution as applied on 2 successive days in ordinary fashion to the contralateral axilla.

1. *Night time application.* Applying the preparation just before retiring contrasted with early morning application on the opposite axilla.

2. *Heat.* (i) Application of infra red radiation from

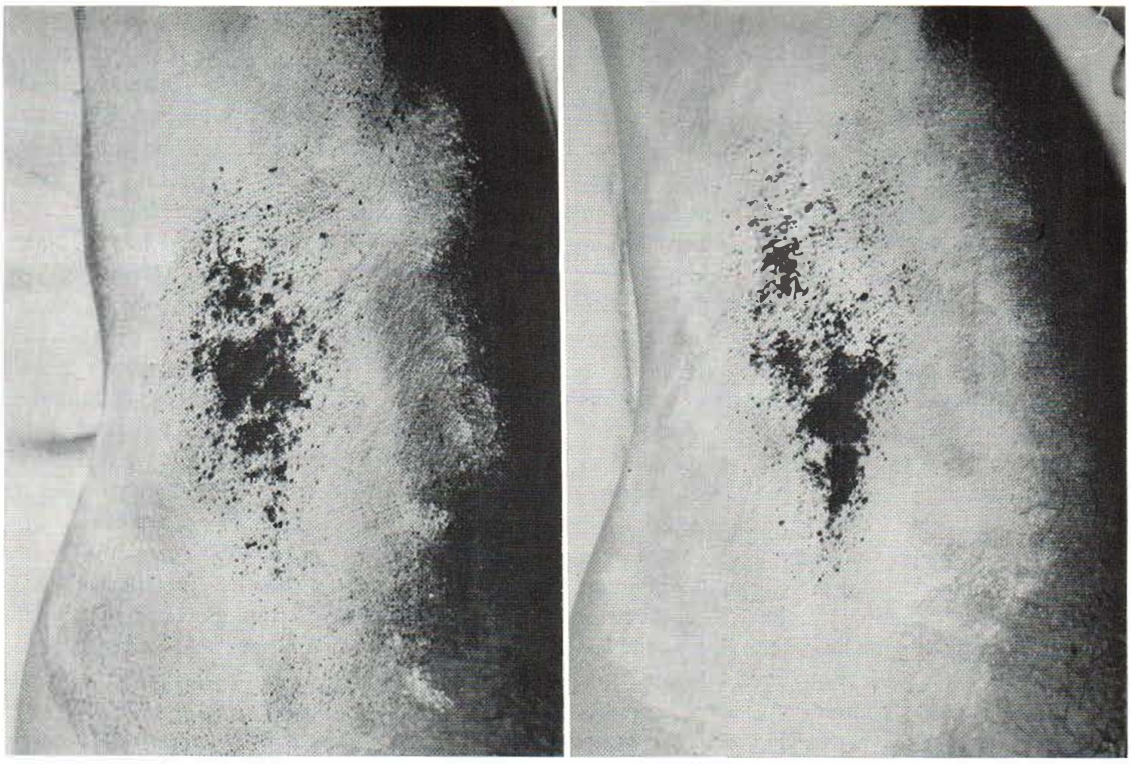

Fig. 2. Absence of antiperspirant effect by commercial aerosol antiperspirant spray on opposite axilla of subject shown in Fig. 1. Before and after photographs of patient's left axilla taken at the same times as those in Fig. 2 serve for paired comparison control. Note that pretreatment photographs of right (Fig. 1) and left axilla (Fig. 2) reveal typical asymmetry of axillary sweat response, the right being greater than left.

heat lamp for up to 4 minutes immediately after application of antiperspirant. (ii) Application of dry hot air stream for 4 minutes from hair dryer to area immediately after application of antiperspirant.

3. *Ultrasound.* Application of ultrasonic vibration to axilla for 30 seconds after antiperspirant applied.

4. *Occlusion.* (i) Application of occlusive Saran wrap® polyvinylidine chloride water vapor impermeable membrane over treated area during day for 8 hours. (ii) Application of silane oils after use of antiperspirant.

5. *Co-catalyst.* (i) Addition of magnesium chloride (1%) to antiperspirant solution. (ii) Addition of hydrochloric acid (1%) to antiperspirant solution. (iii) Addition of gallium chloride (1%) to antiperspirant solution (127).

6. *Surface treatment.* (i) Application of soap film to axilla before applying antiperspirant. (ii) Removal of sebum with petroleum ether and ethyl alcohol before applying antiperspirant.

7. *Removal of iron by chelation.* Use of 1% Tiron® (disodium, 1–2 dihydroxy benzene 3–5 disulfonate) (163) (i) in 10% aluminum chlorhydroxide in hydrophilic ointment, (ii) in 10% aluminum chloride hexahydrate in hydrophilic ointment, or (iii) in 10% zirconyl chloride in hydrophilic ointment. Each was used for 10 days in 5 subjects compared with the appropriate Tiron® free control antiperspirant ointment used for the same period.

B. The trinary system

It was apparent that when aluminum chloride hexahydrate solutions were applied under a variety of conditions, as well as with possible adjuvants, the antiperspirant effect was still limited. None of the therapeutic binary system gave relief to the hyperhidrotic. The armpit of the clothing still became wet under emotional and thermal stress.

The means for control of axillary sweating were not apparent until we observed an unexpected dramatic anhidrosis following a therapeutic interplay of 3 separate conditions. In essence, the clinical

axillary anhidrosis sought by the patient was not achieved simply by an antiperspirant formulation, but rather by a unique trinary antiperspirant system. Each element in this system was essential, and all three were required to act concordantly. Each element had restricted limits which could be defined. Variance beyond these limits or elimination of any of the three elements gave unsatisfactory results.

All of the studies were carried out on from one to 5 volunteer human subjects in whom stress axillary hyperhidrosis occurred to at least a moderate degree. The clinical assessment was based on repeated visual observations in the degree and extent of wetness of the armpit zone of the shirt or blouse at times of stress and/or thermal stress. In each instance, paired control observations were obtained by treating one axilla with commercially available conventional antiperspirant preparations containing either micronized aluminum chlorhydroxide or the aluminum chlorhydroxide propylene glycol complex (Rehydrol®) (99) as used in aerosol units. Also, appropriate bilateral comparisons were made to assess the significance of varying or eliminating elements of the trinary system. Below are detailed the three concordant elements required to achieve total topical control of axillary sweating in hyperhidrotics as well as in normals.

1. *The solution.* The first essential is to have a concentrated, highly ionized aluminum or zirconium salt in an alcoholic solution with a pH of less than 1.0. The most effective preparation was found to be aluminum chloride hexahydrate in a 25% solution in absolute ethyl alcohol. It is made by dissolving the crystals in the alcohol, which at room temperature requires about 3 weeks before complete alcoholysis occurs, and a perfectly clear viscous syrupy solution results. It has a pH below 1.0. We have proven this formulation to have a stability and unimpaired effectiveness as an antiperspirant for over 3 years when stored at room temperature. It was best dispensed in a roll-on glass applicator bottle and applied just to the dry, central vault of the axilla. It may alternatively be put in a unit with a nylon cloth – plastic head applicator. Application by hand was not suitable, because of inadvertent dripping of this highly acidic solution. The application may be made to the shaved or unshaved axilla, but should not be applied to the axilla until 48 hours after shaving, to minimize irritation of minor cuts or scrapes. The solution should not be applied to a wet or palpably moist axilla because irritation will results. The inhalant hazard precluded aerosol dispensing although on an experimental basis with a cone applicator, nylon dip tubes, acid-resistant plastic and dichlorotetrafluoromethane (Freon 114®), it retained its effectiveness.

The concentration of the aluminum chloride hexahydrate could be reduced to 20% or 15%, but at 10% and 5% it lost its effectiveness. Isopropyl alcohol could be substituted as a solvent, using a saturated solution which proved to be less than 15% on a weight volume basis. When water was substituted the aluminum chloride hexahydrate used in 25% solution retained its effectiveness but proved to be irritating. Other liquid vehicles, e.g. *n* propyl alcohol, were found to be less desirable, and the use of creams, pastes, sticks or lotions removed the effectiveness of the aluminum ion. Most importantly, the addition of buffers, reactive chemicals or changing the solvent so the pH was above 1 eliminated the distinctive effectiveness of this antiperspirant. Application of the aluminum chloride hexahydrate powder itself was not satisfactory.

Zirconyl chloride (the octahydrate of zirconium oxychloride) was a satisfactory substituent for aluminum chloride and could be used in either absolute ethanol or isopropyl alcohol in saturated solutions, approximating 20% and 12% respectively. Again, it was found that the pH requisite for achieving axillary anhidrosis was less than 1.0. Other salts of aluminum, e.g. the chlorhydroxide, were not satisfactory; their solutions having a pH well above 4.0.

2. *The occlusion.* The second essential element of the system is occlusion of the axilla for 2 to 8 hours after the application of the anhydrous aluminum or zirconium salt solution. The occlusion is best achieved with a vinyl chloride – vinylidine chloride copolymer sheeting (Saran wrap®), which is essentially impermeable to water vapor (155). Commonly available in 48 gauge thickness (0.00048 inch) it can be applied directly to the axilla either as a closely adherent sheet, or may be bunched into a space filling mass, again filling the axillary vault. It must be kept in close apposition to the skin, and this is best accomplished by wearing well fitted Tee-shirt or a commercial dress shield vest garment. The Saran wrap® could not be attached by tape since this produced local irritation, as a result of the metallic salt.

Polyethylene and other water vapor impermeable

membranes may be substituted but water and water vapor permeable membranes were not satisfactory. The application of vaseline or lanolin or silicones led to inferior antiperspirant effects.

The occlusive membrane is kept in place preferably for 6 to 8 hours. Its use for one hour did not lead to the complete anhidrosis otherwise achievable. After removal of the membrane, the formulation of aluminum or zirconium is carefully washed away and clothing worn without danger of fabric damage.

3. *The inactive gland.* The third and equally essential element is rigid control over the time when the solution and the occlusion is applied and maintained. Success in the employment of the method comes only if the formulation is applied to a dry, non-sweating axilla whose glands remain essentially inactive during the time frame of from 6 to 8 hours. This means practically that the antiperspirant is applied precisely before sleep and remains during the night or period of sleep when physiologically the eccrine glands are inactive.

It is important that the antiperspirant should not be applied to a wet axilla since this leads to irritation. Thus the individual should not shower before application, but rather after the Saran wrap® is removed hours later. Moreover, in tense hyperhidrotic individuals who may perspire even away from the pressures of business, there is a need for being aware that treatment should be deferred until the axilla is dry to palpation. In some a tranquillizer, or an anticholinergic may be initially necessary, in others a late cocktail may suffice. In a few, the topical application stimulates reflex sweating which must be inhibited by giving an anticholinergic agent simultaneously.

RESULTS

In each of the 5 subjects observed, the above type of application and occlusion on 2 successive nights led to a persistently dry armpit, despite mental and thermal stress which produced large areas of wetness in the garment armpit on the side treated with regular commercially available antiperspirant (Fig. 3), (Table II). Furthermore, the complete "anhidrosis" as evidenced by the dry armpit remained for 6 to 7 days without additional treatment. Gradually, sweating returned with an ever enlarging wet spot in the clothing armpit over the subsequent 3 weeks, with return to virtually full sweating function at the end of that time. Retreatment once a week kept the "complete" anhidrosis intact indefinitely. The procedure was effective in the summer when ambient conditions conspire both to favor sweating and to retard evaporation.

Table II. *Inhibition of axillary sweating in hyperhidrotic subject as determined by daily measurement of maximal armpit wetness area under varying thermal and emotional stimuli*

Left axilla: Trinary antiperspirant system: 25% $AlCl_3$ $6H_2O$ in absolute ethanol, pre-sleep application, Saran Wrap® occlusion, three treatments as indicated.
Right axilla: Commercial aluminum chlorhydroxide spray (4 seconds), pre-sleep application, no Saran Wrap® occlusion, twenty-two treatments

Day	Area of shirt wetness (cm^2) Left armpit	Right armpit
Pretreatment		
−2	940	940
−1	340	410
After treatment		
1[a]	0	240
2[a]	0	600
3	0	1 460
4	0	340
5	0	150
6	0	90
7	0	190
8	0	340
9[a]	0	1 460
10	0	600
11	0	340
12	0	940
13	0	150
14	0	340
15	0	600
16	0	410
17	10	150
22	90	240

[a] Treatment of left axilla as above on prior night. No treatment to left axilla on intervening nights. The right axilla was treated as above on each of 22 nights.

The application was associated in 3 of the individuals with tingling and a feeling of warmth. Applications were not made to shaved axillae until after 2 days, to avoid irritation of possible nicked sites. Some branny desquamation was noted occasionally. No miliaria or diffuse erythema was seen. This is in contrast to the miliaria which appears when Saran wrap® alone is used to occlude the skin of the back (46, 105, 140, 160). A slight metallic feel to the stratum corneum could be discerned on washing the treated axilla.

DISCUSSION

The riddle of the axilla has long been—why do topical antiperspirants which will induce a 100%

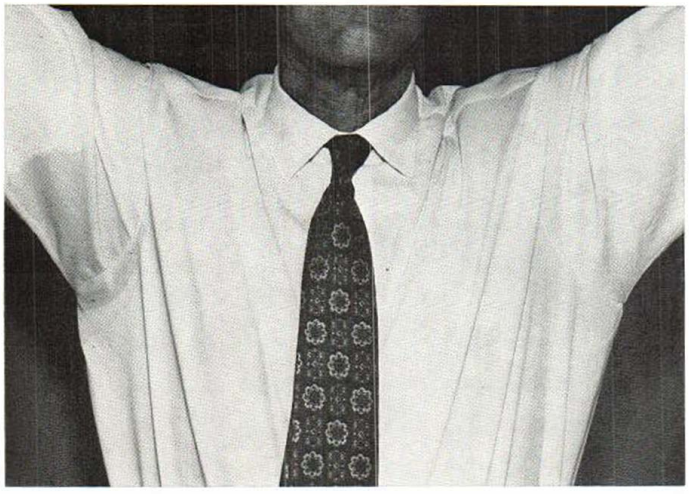

Fig. 3. Antiperspirant effect of trinary system: Maximal thermal and emotional sweat response as monitored continuously by observation of wetness of armpit clothing. Subject's left axilla treated three times by application of 25% aluminum chloride hexahydrate in absolute ethanol to non-sweating axilla at night under Saran wrap®. Photograph after 6 days without any treatment of left axilla. Right axilla served as control, having been treated for the prior 9 successive nights with commercial aluminum chlorhydroxide antiperspirant spray.

anhidrosis elsewhere produce only a 50% reduction of sweating in the axilla? Why does an anticholinergic compound applied under plastic wrap occlusion fail to produce anhidrosis in the axilla (50) when it regularly induces complete anhidrosis elsewhere? Our experiments provide the answer. It is not that the axilla has unusually large or inaccessible sweat pores. It is not that the sebaceous (121) or apocrine secretions or soap (5) in the area block the antiperspirant. Rather the riddle of the axilla is in its own sweat.

Here is an area continually washing away, flushing and diluting any antiperspirant applied. It is for this reason that antiperspirants have been so relatively ineffectual in this zone and particularly in the hyperhidrotic. To be effective, metallic salt antiperspirants require prolonged contact with the skin. they do not act instantly and hence any antiperspirant applied during the day is flushed away from its poral target site by the casual intermittent stress sweating of that day. Noteworthy is the fact that objective antiperspirant testing as a daytime procedure done experimentally or commercially on volunteers within the time frame of 8 a.m. to 5 p.m. Furthermore, most consumers either apply the antiperspirant in the early hour toiletry or just before the critical social event, with the expectation of instantaneous action. In these circumstances the antiperspirant has but little chance of ionic contact with the critical terminal duct area. Only the more acidic preparations come with the label, to apply at night, a caution to circumvent the destruction of clothing fabrics which would otherwise follow daytime use.

But mere application at night does not insure the desired anhidrotic effect. The critical factor is the prolonged intimate contact with the antiperspirant during a period of essentially non-sweating. This must be of the order of 6 to 8 hours, and hence the sleep period is most practical since we have observed during sleep eccrine gland function is virtually absent. The axilla remains dry, autonomic input being minimal unless the environment poses a severe thermal stress. Nor does mere application and prolonged contact of an antiperspirant in the non-sweating axilla insure inhibition of sweating. It only allows the antiperspirant the opportunity to enter and to remain within the terminal eccrine duct. And hence it was not until we abandoned day time testing that we had the chance to work further into the riddle of the axilla and learn that it had not this just one but rather three parts. Each was essential.

The second critical item in formulating an effective axillary antiperspirant system proved to be the antiperspirant itself. Its formulation called for a concentrated solution of either aluminum chloride hexahydrate or zirconyl chloride, preferably in absolute ethanol or isopropyl alcohol. Although our studies are too limited to definitively distinguish these two vehicles, absolute ethyl alcohol proved to be excellent. A 25% crystal clear solution of aluminum chloride hexahydrate could be prepared by allowing the crystals and solvent to stand at room temperature for 3 weeks. During that time apparently alcoholysis took place, and the resultant solution proved on testing to be stable and effective for over a three year period. The salt solution had a degree of viscosity which favored application with a roll-on

unit with fine tolerance. The fragrance was pleasing and this is important to the fastidious since the very high intrinsic pH of the solution precludes the direct addition of perfumes. The material quickly dried on the axillary surface to form a smooth powdery film. Inexpensive, safe, non-allergenic, absolute ethyl alcohol provided a good nethod of anhydrous application. It is further probable that the alcohol dehydrated the keratin, promoted absorption into the duct and favored chemical interaction.

The resulting pH of the solution had to remain at pH 1.0 or below. The addition of buffers or reactive compounds to reduce the acidity reduced the efficacy. This is in keeping with the fact that the more acidic the preparation, the most effective it is as an antiperspirant. A 10% aqueous solution of zirconyl chloride with a pH of 0.8 is one of the strong antiperspirants but remains a laboratory curiosity (27), whereas a similar solution of the aluminum chlorhydroxide complex with a pH of 4.0 is far less effective as an antiperspirant, but is used in dozens of commercial antiperspirants. To lower the pH one has the options of increasing the salt concentration (158), using ethyl or preferably isopropyl alcohol in place of water (59), or substituting zirconium for aluminum (27). Manufacturers have knowingly had to sacrifice antiperspirant efficacy by raising the pH of the preparation to protect the user's clothing from acid rot. Cream, lotion, and stick preparations apparently reduced the ionic strength and so were ineffective. Water could be used as a solvent but its use tended to be associated with primary irritancy reactions, possibly due to the fact that wet stratum corneum renders the skin more susceptible to chemical irritancy.

Indeed it appeared that our antiperspirant, a formulation always considered far too acidic for any use, was able to sail between the Scylla and Charybdis of skin irritancy and clothing destruction. The charting of such a course required not only the anhydrous application of the metallic salts to the dry non-sweating axilla, but the addition of the third and final element essential to this antiperspirant system, viz. an occlusive covering. This was the vinyl chloride vinylidine chloride membrane or Saran wrap®. Further awareness that it is not enough to apply a powerful antiperspirant to the dry non-sweating axilla came from our experiments with the anhydrous aluminum chloride and zirconium tetrachloride. These were compounds from the world of the Friedel-Craft reactions (98), not only powerful but water activated (67). Their reactivity was maximal at the "wet spot" of the sweat pore. Yet despite their superiority to all other compounds we had studied, they failed to give "garment dry" anhidrosis under maximal stress stimuli to the sweat gland. This was true even when applied in ethyl ether, wherein anhydrous aluminum chloride retains its monomeric form with full water reactivity (98).

Apparently the metallic salt must actually enter and remain in the terminal sweat duct, since the chemical reaction is not rapid. It is here that the water vapor impermeable membrane solves the final problem in this technology of topical application, specially directed to the sweat gland. Saran wrap® is excellent, being thin, resistant, highly impermeable and non-inflammable (155). The generally available film is 48 gauge, i.e. 0.00048 inch in thickness. Equally important, it is completely resistant to the low pH and the alcohol and the hydrochloric acid present. Polyethylene (Handi-Wrap®, Glad Wrap®), although more permeable, were also satisfactory. To achieve the effect the Saran wrap® must be in close apposition with the axillary skin surfaces. Finely crumpled wads can be snugged into the axilla under a night garment or sheets introduced between the skin and a well fitted dress shield unit. Tape cannot be used. Saran wrap® in gauges above 100 proved too thick for easy manipulation. The Saran wrap® is removed after the sleep period and the axillae carefully washed with soap and water to remove surface aluminum chloride. At this time, very fine droplets of antiperspirant can be seen on the Saran wrap® under surface, demonstrating the completeness of occlusion.

Again it must be stressed that Saran wrap® occlusion alone will not produce anhidrosis. Indeed, even using aluminum chlorhydroxide solution under Saran wrap® does not lead to complete anhidrosis. All three elements—the dry non-sweating axilla, the concentrated acidic aluminum or zirconium chloride solution and the totally occlusive covering—are necessary.

What is the mechanism of the antiperspirant effect of these metallic salts? Our current view is that:

1. The effect is mediated through the aluminum or zirconium ion, hence the need for the most highly ionized form. Note that aluminum is the best protein denaturant of the metallic ions, as little as 0.0002 M

being effective (71). Note that it attaches to keratin combining with the COOH (38). Possibly the acid acts as a catalyst. Incidentally, the antibacterial action of the aluminum ion (9) precludes the development of miliaria.

2. The effect is slow, taking from 24 to 48 hours for fruition. Note that strong electrolytes require several days for penetration into cadaver skin, and that they do this via the sweat duct (79). Furthermore, acid alcohols may require the same period in vitro to combine with proteins (108). The action is not an immediate pharmacologic one.

3. The effect is superficial yet not in the stratum corneum. Intact skin is highly impermeable to the aluminum ion. Virtually none is found in the dermis (8). The aluminum ion is not acting on the nerve, secretory acini, nor dermal duct. It remains in the stratum corneum, and the upper terminal sweat pore. The site of critical action is not in the stratum corneum since Scotch tape stripping off of the stratum corneum of an anhidrotic area does not return sweating to normal as it would if the blockade were superficial and in the stratum corneum.

4. The effect takes place within the terminal sweat duct. The aluminum ion enters by capillarity and by reflux during minimal intermittent sweating. The pore of the sweat gland is viewed as being functionally closed until a sweat droplet forces egress. It is, as it were, a sphincter which guards the duct—inapparent even on surface electron scan microscopy—indeed the duct itself is like the pleural space—an abstraction until sweat flows through it. Otherwise it lies collapsed—inapparent in the fixed pathologic section; open and evident only as the sweat passes. Just as air and sweat may reflux back into the duct (80, 92) so we feel does some of the aluminum ion. It has an ionic radius of only 0.5 Å (106), being one of the smallest cations; so that favors inward passage, not only with the sweat pore but into the keratin molecule itself. Furthermore the isoelectric point of keratin is 2.2 so that its charge, normally negative, is reversed to positive when employing a pH below this, thereby reducing a presumed electrical barrier (116).

5. The aluminum combines with the intraductal keratin fibrils, producing a functional closure, a supercontraction not apparent histologically (122). The fixed keratin remains as an obstructive block to free egress of sweat until it is shed several weeks later. The ducts with the narrowest ostia close first. Miliaria does not develop since bacteria are not present, having been destroyed by the aluminum or zirconium ion. Accordingly, there is no rupture of the wall of the duct with secondary inflammation. The intraluminal pressure rises to the point where it acts as a feedback system, shutting off acinar secretion.

6. Although the primary antiperspirant event is a protein closure of the terminal duct, in the subsequent days increased intraductal as well as surface keratinization may be induced by the aluminum ion, leading to clinical scaling as well as to a histologically visible keratinous plug—and trapped PAS-positive mucopolysaccharide material secreted by the dark cells.

The technique we have described is useful. Two applications followed by one treatment a week affords "garment dry" anhidrosis. The patient needs to be educated as to the need for more than a squirt of an aerosol, and some must be alerted to the fact that complete anhidrosis localized to the axillae is not harmful. The gland has no essential excretory function, nor does the removal of these glands decrease the individual's heat tolerance (69). The procedure is safe and non-allergenic. Irritation if it develops is minor, transitory, and only suggests caution in making certain the preparation is applied immediately on retiring rather than in the evening.

We have found the same technique equally useful for inhibiting sweating of hyperhidrotic palms and soles in fifteen patients, although more frequent applications are necessary. It may find use in the treatment of localized hyperhidrosis of other areas (148) including the crural region.

Our experiences have demonstrated to us that the proper subject for the study of axillary antiperspirants is the axilla of the hyperhidrotic. Screening tests may be done on egg albumin (48), casein (20), frog skin (146), the mouse foot pad (74), the forearm or back (162), but relevant useful data still must be secured by observing the effects on the axilla of the individual afflicted with the problem. (73.) We also would stress the usefulness of using the "shirt test". Simple observation of the armpit wetness allows a simple practical assessment of considerable appeal and significance to the consumer. Finally, future studies of axillary antiperspirants must take into account the functional state of the eccrine glands at the time of the antiperspirant application and for hours thereafter.

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