

# The Action of Antiperspirants

CHRISTOPHER M. PAPA, M.D.\*

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**Synopsis**—Stripping experiments, methylene blue iontophoresis, and histological studies after induced sweating indicate that formaldehyde forms a physical plug in the sweat duct. On the other hand, similar experiments with aluminum chloride treated skin suggest that this antiperspirant acts by altering the permeability of the sweat duct.

Our fastidious population indulges in a significant amount of concern about those usually private recesses, the axillae. Women require the area be denuded of hair, and both sexes apparently wish the underarms dry and odor free. While cold steel swiftly decides the fate of the useless pelage, the chemical attack on axillary perspiration remains unsure. If the compound to be applied has bacteriostatic properties, it will succeed as a deodorant since it retards the microbial growth which produces the offensive odor (1). Usefulness in sweat suppression, however, is a more vexing problem.

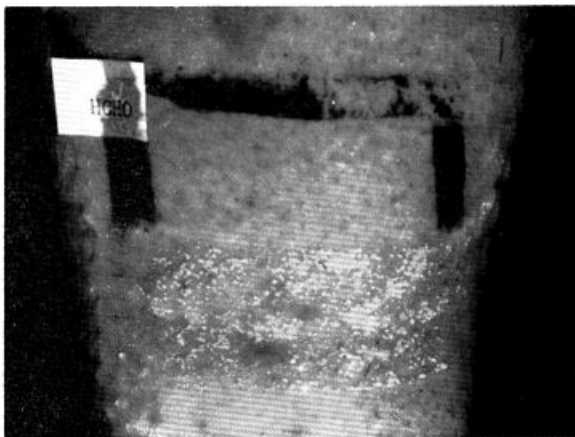
The eccrine sweat glands contribute the major portion of secretory products in the axilla. Therefore, interest has centered on chemicals which might produce anhidrosis, interference with the production or delivery of sweat to the skin surface. Both formalin and aluminum salts have been employed for this purpose for some time, without sure knowledge of their modes of action. The popular concept is that both

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\* Department of Dermatology, University of Pennsylvania, School of Medicine, Philadelphia, Pa. 19104.

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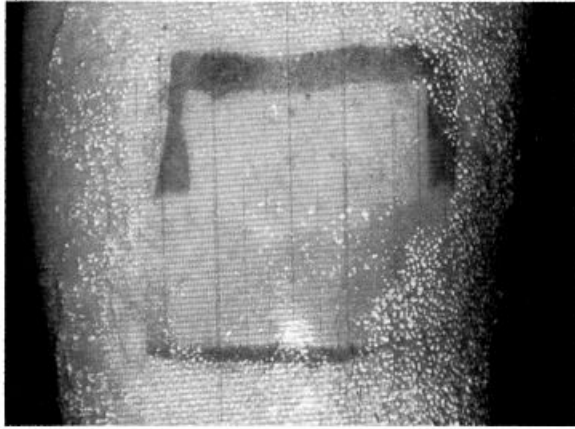
*Figure 1.* Anhidrotic square of skin following treatment with 10% formalin solution. The lower half of the area has been stripped to remove stratum corneum using cellophane tape. Following thermal stimulation sweat appears in the stripped area only as the superficial obstruction is relieved. The skin has been painted with a starch-castor oil suspension, and the perspiration shows as white droplets

produce some type of plug at or near the skin surface, occluding the eccrine ostium and preventing the exit of perspiration (2, 3). Formalin introduced into the skin by iontophoresis has also been reported to inhibit glandular secretion directly (4). Unable to find evidence for plugging, Sulzberger, *et al.* suggested that aluminum worked in an entirely different manner. An inflammatory infiltrate, found about the intraepidermal and high dermal portions of the duct, was thought to interfere with transport of the sweat (5). This action was said to result from "chemotaxis." By the use of sensitive *in vitro* studies, however, Blank, *et al.* concluded that aluminum did not penetrate into dermal tissue (6). It was with the hope of resolving these contradictory views that the following study was initiated.

#### EXPERIMENTAL

##### *Production of Anhidrosis*

Twenty healthy men served as subjects. Square gauze pads (5 cm), with either 10% formalin, 20% aluminum chloride (hexahydrate), or distilled water, were placed on the volar surfaces of forearms under an occlusive dressing of Saran Wrap<sup>®\*</sup> and Clear Tape<sup>®†</sup> overnight for 18 hours. Following removal of these patches, the men were exposed to



*Figure 2.* Area of volar forearm treated with aluminum chloride solution remains anhidrotic even though the lower half has been stripped to remove the horny layer. It would thus be unlikely that a superficial block is operating in this instance. The few sweat puncta appearing in the stripped site reflect the unmasking of the anhidrosis produced by the aqueous vehicle

38°C and 90% relative humidity in a controlled heat chamber. Sweating was demonstrated by painting a starch-castor oil mixture over the skin; droplets of perspiration are observed as white puncta on the surface (7). Initially all treated areas are anhidrotic, but within an hour the water site gradually recovers sweating as the skin dries. All subsequent test procedures in the formalin and aluminum areas, therefore, were carried out only after allowing time for the effects of simple hydration to disappear. When undisturbed, the aluminum and formalin anhidrosis was complete for 3 to 4 days, slowly returning to normal within 7 to 14 days. The following experimental maneuvers were then carried out on the anhidrotic sites to determine how each agent had brought about sweat suppression.

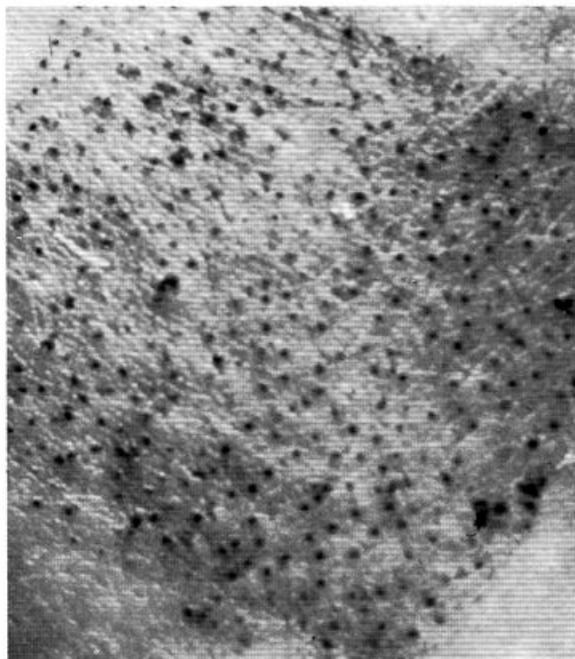
#### *Horny Layer Removal*

Half of each anhidrotic test site was stripped with Scotch Tape<sup>®†</sup> until the major portion of the stratum corneum was removed and the "glistening layer" was reached. Coupled with the visual estimation of

\* Dow Chemical Co., Midland, Mich.

† Johnson & Johnson, New Brunswick, N. J.

‡ Minnesota Mining Co., St. Paul, Minn.



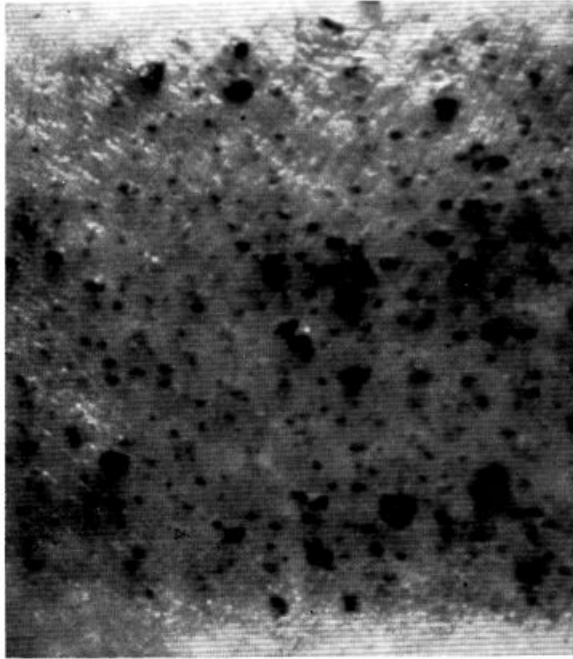
*Figure 3.* Methylene blue pattern produced by iontophoresis into normal skin. This is the typical, specific pattern normally obtained. Each punctum represents passage of dye down the duct and diffusion into the surrounding epidermal tissue

sweating, this technique immediately demonstrates whether a superficial plug is actually present. Removal of the horny layer to relieve such blockage would allow prompt return of normal sweating.

Stripping of both the water and formalin treated sites brings perspiration back to the previously dry skin (Fig. 1). The aluminum-salt treated area of anhidrosis, on the other hand, showed little except a few droplets, representing no more than reversal of residual hydration effect (Fig. 2). The tentative conclusion was that formalin and water did actually produce some type of block within the stratum corneum, while the cause of aluminum anhidrosis was deeper in the skin.

#### *Methylene Blue Iontophoresis*

When methylene blue dye is introduced into the skin by iontophoresis, a typical punctate pattern develops which is entirely localized about the eccrine ducts (Fig. 3). This staining represents transport of the dye down the eccrine ducts and diffusion through the duct wall into the



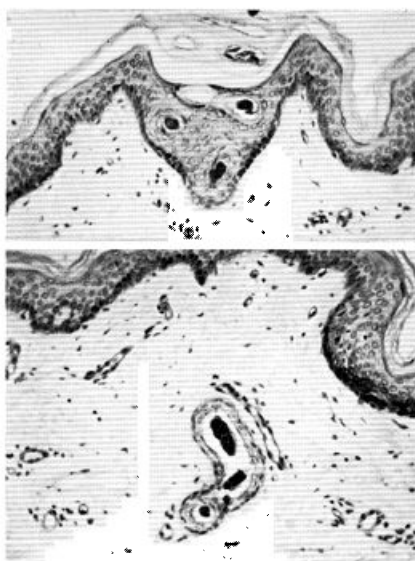
*Figure 4.* Methylene blue iontophoretic pattern in aluminum salt treated area. The coarse, darker puncta are produced by greater transductal permeation of the dye and more extensive epidermal staining

surrounding epidermal tissue (8). To accomplish this, the sweat glands must be active and their lumina patent. To test for these conditions, an attempt was made to produce pore patterns in the formalin and aluminum sites of anhidrosis. Thus, after the obligate one hour delay to negate the effects of hydration, a 0.1% methylene blue solution was iontophORIZED into the treated areas using 0.5–0.75 ma/cm<sup>2</sup> for 5 minutes.

It was not possible to produce an eccrine pore pattern in the formalin treated skin. Since the stripping experiment already demonstrated superficial blockage, passage of the dye into the ducts was not expected. In the aluminum-salt treated site, however, not only was the characteristic blue pattern present, but the puncta were sharper and larger (Fig. 4). It was thus ascertained that the ducts were patent and the glands functioning. As regards the augmented pattern, it was shown that this was due to increased transductal permeation of the methylene blue and wider diffusion into the surrounding epidermis. It now remained for histologic studies to verify these gross observations.



*Figure 5.* Biopsy of formalin treated skin before forced sweating. Amorphous material is seen plugging the uppermost coils of the duct within the stratum corneum. These masses are removed by the stripping procedure and allow sweat to flow onto the skin surface again. Note that the duct is not dilated. (H. & E. 250 $\times$ )



*Figure 6.* Formalin treated site after sweat stress, demonstrating distension of the sweat duct and accumulation of intraluminal masses of PAS positive diastase resistant material. These serial sections show the depth and extent of the ductal dilatation resulting from sweating into the plugged eccrine unit. Note the absence of periductal inflammation as seen in aluminum anhidrosis. (PAS with diastase digestion  $\times 100$ )

#### *Effect of Forced Sweating in Anhidrotic Sites*

Biopsy samples from each treated, unstripped, anhidrotic site and control volar forearm skin were obtained from five subjects immediately after removal of the occlusive patches. The men were then sweated for one hour and repeat specimens taken from sites adjacent to the prior biopsy. Tissues were fixed overnight in 10% neutral buffered formalin and sections stained with hematoxylin and eosin (H. & E.) and periodic Acid-Schiff (PAS), with and without diastase digestion.

The purpose of the sweat stress imposed on the subjects between the biopsy procedures was to assess the functional state of the secretory glands and to observe the effect of forcing perspiration into a duct which in the case of formalin treatment was presumed occluded, but more susceptible to transductal permeation in the case of aluminum salt induced anhidrosis.

A. *Formalin*—Pre-sweat samples in the formalin treated areas were characterized by the presence of amorphous intraluminal masses of eosinophilic material plugging the superficial coils of the eccrine duct (Fig. 5). These intraluminal masses were not PAS staining. The dermal and intraepidermal portion of the ducts appeared patent and normal. A good complement of PAS positive (diastase digestible) glycogen was contained in the secretory coil.

Following the heat stress, biopsies from the same areas showed a marked change in the microscopic picture. Ducts were widely dilated

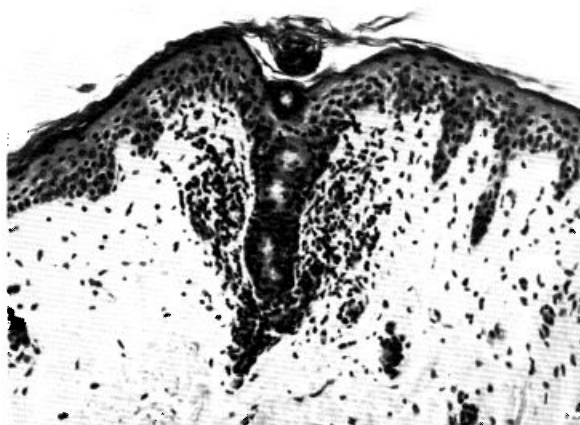
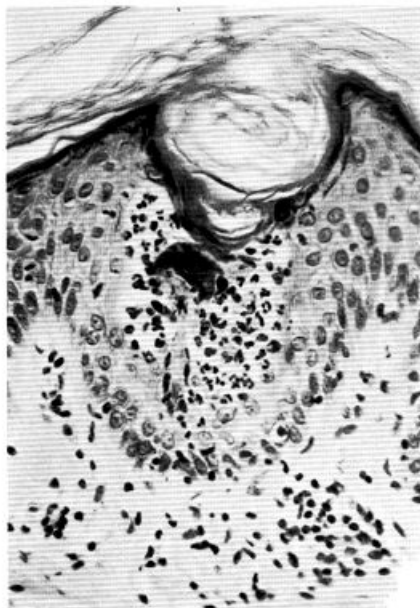


Figure 7. Periductal inflammation in aluminum salt treated skin after one hour sweating. The eccrine unit is otherwise normal without ductal dilatation. The "plug-like" appearance of the horny layer is an artifact of sectioning. Pre-sweat samples of this skin are without inflammation, leading to the conclusion that perspiration pouring into the dermis invites the reaction. (H. & E.  $\times$  100)

throughout their entire epidermal course and occasionally deep into the dermis. Intraluminal masses of PAS positive (diastase resistant) material, not seen in the pre-sweat samples, now were present along the length of the duct (Fig. 6). In the past this material was thought to play a role in the development of sweat retention and miliarial lesions (9), but it is more likely a secondary event due to the superficial obstruction present. Granules of the PAS positive (diastase resistant) substance are normally secreted by the sweat glands (10), and since the material cannot escape onto the skin surface when the duct is blocked it tends to accumulate intraluminally.



*Figure 8.* Skin biopsy from area of aluminum salt induced anhidrosis. Ductal rupture and leakage of sweat within the epidermis produce the acute inflammatory infiltrate. Note that the superficial coils above the lesion are patent, and the duct is not dilated. Clinically these lesions resembled the prickly heat rash (H. & E.  $\times 250$ )

Both the dilatation of the ducts and the appearance of the PAS positive nonglycogen material speak for continuing glandular function in the anhidrotic skin. Further evidence is seen by the disappearance of glycogen, the PAS positive diastase digested substance, from the secretory cells. In contrast to the pre-sweat samples, those specimens taken after the forced sweating show depletion of this material.

It is appropriate to comment that both the pre- and post-sweat samples taken from the water treated skin sites were identical in histologic appearance to those obtained from the formalin areas, with but one important exception. No discernible physical plug was present in the hydrated skin which could explain the high level blockage. This is not an unexpected result since poral closure by water is a temporary, functional event due to swelling of the horny layer cells at or near the eccrine ostium (11, 12).



*B. Aluminum*—Skin obtained from the areas of aluminum salt induced anhidrosis before the subjects were sweated was normal. No plugs or casts were seen, the ducts were not dilated and there was no evidence of inflammation. The secretory coil contained abundant glycogen. Following the hour of forced sweating, a striking picture had developed. A well formed infiltrate of polymorphonuclear and lymphocytic leukocytes localized in the periductal tissue about the epidermal-dermal junction, where the eccrine duct traverses the rete peg (Fig. 7). Occasionally the infiltrate involved the epidermis and duct wall, coincident with spongiotic changes. This represented incipient miliarial lesions (see below). Glycogen disappeared from the secretory coil after the thermal stress, verifying normal glandular secretion.

The above sequence of histologic events are interpreted as demonstrating that aluminum chloride produces anhidrosis by altering the permeability or resorptive function of the epidermal portion of the eccrine duct. Under conditions of forced sweating the perspiration pours into the dermis faster than it can be cleared, inciting the periductal inflammatory reaction. This concept is supported by the demonstration of increased transductal permeation of iontophoresed methylene blue. It also explains why the stripping maneuver is ineffectual in restoring perspiration in aluminum anhidrosis.

Finally, it is to be reported that 3 of the 20 subjects developed scattered erythematous papules in aluminum salt treated areas only. These lesions erupted beneath the patch and closely resembled prickly heat or miliaria rubra. This diagnosis was confirmed on biopsy, which showed intraepidermal vesicles about the sweat duct, with an acute inflammatory reaction (Fig. 8). Finding miliaria only in aluminum chloride treated skin also speaks for a mechanism whereby damage to the intraepidermal duct, either anatomic or physiologic, permits transductal escape of sweat.

## DISCUSSION

Superficial obstruction of the eccrine outlet has long been favored as an explanation of how spontaneous sweat disorders develop as well as how antiperspirants produce anhidrosis. The same mechanism has been indicted in sweat retention complication in the chronic dermatoses such as psoriasis and atopic dermatitis (13, 14). Such high level blockage, regardless of the cause, may be demonstrated by the following procedures: *i*, removal of the stratum corneum relieves the obstruction, bringing about an immediate return of sweating; *ii*, occluded eccrine ostia prevent

development of the eccrine pore pattern produced by the iontophoresis of methylene blue; and *iii*, forced sweating into the obstructed ducts causes wide dilatation and the accumulation of PAS positive diastase resistant material. The actual nature of the occlusion is quite variable; in the chronic dermatoses it is a hyperkeratotic or parakeratotic plug, in formalin produced anhidrosis an intraluminal mass resulting from the protein precipitant properties of the chemical. In the sweat suppression by hydration, a functional poral closure alone is operative.

Aluminum anhidrosis meets none of the requirements that demonstrate a high level blockage. Removal of the horny layer does not reverse the sweat suppression and, rather than preventing formation of the methylene blue pattern, actually facilitates the staining. Forced sweating, rather than producing ductal dilatation, leads to periductal inflammation and, in extreme instances, ductal disruption as in miliaria rubra. This total picture suggests that aluminum salts alter the epidermal duct and permit large amounts of sweat to pour into the surrounding tissue. Perspiration will not reach the skin surface, in the same way that a multi-punctured garden hose, regardless of the head of pressure, prevents water from reaching the nozzle. Interestingly, Sulzberger (5) had described the same histologic findings in his studies on aluminum salt anhidrosis. Without employing the sequential biopsy technique and forced sweating as above, he concluded that the leukocytic infiltrate resulted from the "chemotaxis" of aluminum or its products and that the inflammation then interfered with ductal transport of sweat.

Finding miliarial lesions in several subjects parallels Shelley's experience with aluminum salt anhidrosis (3). This does not, however, mean that one should regularly expect to find rashes produced by underarm deodorants. As a matter of fact, these agents, primarily composed of aluminum salts, rarely cause such effects in practice. The explanation for this paradox rests in the fact that experimenters wisely choose glabrous skin such as the forearm or back, not the axilla, to study eccrine anhidrosis. While aluminum efficiently prevents perspiration in these areas, its effects in the underarm area are reduced. Miliaria probably does not develop because the chemical does not exert its full effect. The reason for the failure is not clear. The forehead is another resistant area (15), and it is interesting that both these regions (as well as the palmar surface) also do not permit easy development of eccrine pore patterns with methylene blue iontophoresis (8). It is necessary to state that these areas share a common difference which distinguishes them from the remainder of the body: The eccrine glands of the axilla, forehead, and

palm respond primarily to emotional rather than thermal stimuli. There is no evidence for anatomical differences between the eccrine units of the body. Therefore another yet unidentified variable is to be sought.

#### SUMMARY

Local eccrine anhidrosis was produced in human volunteers by application of 20% aluminum chloride, 10% formalin solutions, and water itself, under occlusive patches. It can be demonstrated that the sweat suppression of simple hydration and formalin is due to a high level obstruction of the eccrine duct. Removal of the stratum corneum relieves this type of anhidrosis. Methylene blue iontophoresis fails to produce a sweat pore pattern since the dye cannot enter the ducts, and there is histologic evidence of ductal dilatation following sweating into the closed system. A physical plug can be seen in the case of formalin induced anhidrosis, while the water effect is temporary and due to a functional closure of the eccrine ostium.

In aluminum salt produced anhidrosis, stripping off the stratum corneum does not bring about return of sweating, and an accentuated eccrine pore pattern results from the iontophoresis of methylene blue. Only after sweating is there an inflammatory infiltrate localized in the periductal tissue surrounding the eccrine duct at the epidermal-dermal junction. It is concluded that aluminum chloride increases transductal absorption of sweat.

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