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Mechanism of antiperspirant action of aluminum salts

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Synopsis

Complete anhidrosis was induced by occlusive application of aluminum chloride hexahydrate for 3 and 24 hr. Immediately after exposure, an amorphous aluminum-containing cast was demonstrated in the sweat ducts by the fluorescent morin stain. The cast was PAS-positive, diastase-resistant and extended throughout the acrosyringium down to the upper and mid-dermis. Histologically, the luminal cells of the acrosyringium were damaged and soon sloughed, fusing with the cast. There were no inflammatory changes. The physically occluded ducts did not sweat for two to three weeks until the normal process of cell renewal resulted in replacement of the acrosyringium. ANHIDROSIS induced by ALUMINUM SALTS has unique characteristics which distinguish it from all other procedures which interfere with sweat delivery.

INTRODUCTION

Of a great variety of metallic antiperspirant salts, aluminum chloride, introduced by Stillians in 1916 (1), is still the most effective. More than 60 years later it is startling that there is virtually no agreement regarding the way in which aluminum chloride, or a host of other metallic salts, brings about inhibition of eccrine sweating. This is not because of lack of interest. Fiedler's sturdy review (2) of the antiperspirant literature lists 411 references! Writings on the mode of action provide a vivid panorama of disparate observations and contrary conclusions. The field is a battleground of contentions and confusions. Despite intensive study by sapient scientists, the prevailing ideas are almost wholly speculative. Investigators have sweated mightily, but the problem is as slippery as ever; the sweat apparatus refuses to yield its secret.

The most ancient theory ascribes antiperspirant activity to astringency, that is, simple shrinkage of the pore. It is subjectively appealing to imagine that the low acidity of aluminum chloride (pH = 2.0) can shut off the flow of sweat by contracting the orifice. However support for this idea rests on pharmacologic folklore, not scientific observations.

Attempts have been made to salvage the astringency theory by showing that acidic aluminum salts can precipitate proteins; the latter could obstruct the flow of sweat. However, a number of chemicals which form strong flocculants with proteins, for example, tannic acid and sulfosalicylic acid, have minimal antiperspirant activity.

Besides, aluminum sulfate is a poor antiperspirant even though its protein-precipitating ability is equivalent to aluminum chloride (3).

The first experimental effort to explain the anhidrotic effect of aluminum salts was made by Sulzberger, Zack & Herrmann (4). They applied a cream containing 20% aluminum sulfate to the axilla of eight subjects at 12-hr intervals for three applications. Histologic examination showed an intense periductal inflammatory reaction in the dermis, primarily consisting of neutrophils with a variable mixture of lymphocytes. These cell later appeared in the lumen in large numbers. Concomitantly, degenerative alterations in the aprocrine glands were noted. These workers suggest that neutrophils are attracted to the ducts by chemotactic activity of the aluminum salt. These observations remain unverified and are all the more remarkable since aluminum sulfate is a feeble antiperspirant.

Another version was soon proffered by Sulzberger and his co-workers (5). They postulated that the sweat duct possessed an electrophysiologic gradient which was most negatively charged toward the surface. Hence positively charged electrolytes would nullify the gradient and inhibit sweating, while electro-negative ones would be enhancing. This quixotic notion has so many inconsistencies that experimenters by and large have not stirred themselves to a refutation.

Then came the classic experiments of Shelley & Horvath (6,7). They produced miliaria in a variety of ways, viz., ultraviolet radiation, heat freezing, iontophoresis and application of aluminum chloride. Their view was that the histopathologic picture was the same regardless of the way in which miliaria had been provoked, namely, hyper- and parakeratotic plugs within the sweat duct orifices. We have recently reviewed in detail the history of the plug theory (8). Suffice it to say here that the idea is no longer tenable. The horny plugs are a response to injury and are part of the repair process. They follow miliaria but are not its cause. Plugs have not been observed in the stage of anhidrosis which precedes miliaria. Papa & Kligman (9) noted that many of the photographs purporting to show plugs merely demonstrated the normal architecture of the sweat pore. The terminal intra-corneal spirals of the duct wind through a "beaker" of horny material, which indeed resembles a plug but is perfectly normal.

Still another theory holds that aluminum chloride affects the secretory portion of the sweat gland, preventing the formation of sweat rather than impeding its delivery to the surface. Shelley (10) has disproved this possibility by showing that glycogen disappears from the secretory coil beneath the miliarial lesion, a reliable sign of active sweat secretion. Besides, miliaria cannot occur except by the extravasation of sweat into the peri-ductal tissue.

Brun et al. (11) postulated that aluminum salts produced epidermal thickening (acanthosis) and that this made it difficult for sweat to escape. However, Hunziker et al. (12) showed with a variety of organic acids, aldehydes and alcohols that there is no correlation between antiperspirancy and acanthogenicity.

Without doubt, the strangest theory of all was proposed by Papa & Kligman (9). Because they could not find a plug, could not relieve the anhidrosis by stripping but could obtain methylene blue pore patterns, indicating at least partial ductal patency, they contrived the leaky-hose hypothesis. According to this triumph of deductive reasoning, an obstruction did not exist. Instead, sweat poured through a duct made

leaky by aluminum and was resorbed at the same rate. Water never reached the nozzle but leaked out along the way!

Recently, Shelley & Hurley (13) seemed predisposed to revive the horny plug theory in a modified form. They stated that

> "... aluminum combines with the intraductal keratin fibrils, producing a functional closure, a supercontraction not apparent histologically. The fixed keratin remains as an obstructive block to free egress of sweat. ..."

Keratin fibrils, of course, are encased within cell membranes and not free within the ducts.

The most edifying work to date is that of Reller & Luedders (14). They demonstrated an aluminum-containing mass within the epidermal portion of the acrosyringium. They postulated the formation of polymeric hydroxide gels by the slow neutralization of acidic metallic salts. They were able to correlate antiperspirant activity of a large number of metallic salts with their capacity to form gels within millipore filters previously immersed in solutions of the test agents and subsequently exposed to ammonia vapor. They measured manometrically the resistance to the flow of water through the treated filters. A gel was presumed to have formed in the pores of the filter when there was increased resistance to the flow of water. They found that salts whose pK's (dissociation constants) were well on the alkaline side, completely lacked antiperspirant activity. Only acidic salts could form gels. Although our observations are divergent in some particulars, Reller & Luedders were the first to demonstrate an obstruction in the form of an aluminum-containing cast within the acrosyringium. We have fully confirmed this important observation and wonder how it has eluded detection up to now, since the cast can be visualized even by ordinary H&E staining.

Our intention in this paper is to show that aluminum anhidrosis is distinctive and results from a physical obstruction accompanied by cell damage.

MATERIALS AND METHODS

SUBJECTS

These were 60 healthy, young adults of both sexes, predominantly Caucasian. They signed informed consent forms and were paid for volunteering.

TEST CONDITIONS

The test areas were either the volar forearm or the lower back. The studies were conducted from October to May to avoid interference from excessive perspiration during the hot summer months.

APPRAISAL OF SWEAT INHIBITION

A modification of Sarkany & Gaylard's (15) imprint technique was utilized. Brisk sweating was induced by putting the subjects in an environmental chamber at 55°C and 30% R.H. After drying the test site with a cloth, a highly viscous mixture of a silicone monomer and a catalyst (Syringe Elasticon®, Kerr Co., Romulus, Michigan), at

a ratio of 40:1, was spread thinly over the surface with a wooden tongue depressor. Under our conditions the mixture polymerizes within about 5 min. Emerging droplets of sweat form bubbles in the hydrophobic silicone after which the rubber sheet can be gently pulled from the skin and kept as a permanent record. By viewing the imprints in transmitted light, the proportion of nonpatent ducts can be estimated in relation to a nearby control site of untreated skin. The degree of hypohidrosis was assessed to the nearest 25%, as previously described (8).

A comparison of this global assessment with actual sweat gland counts, obtained by projecting the imprints onto a screen, showed excellent correlation with an error of less than 10%.

KINETICS OF ALUMINUM CHLORIDE ANHIDROSIS

Each investigator seems to have used a different methodology with a variety of aluminum salts at various concentrations. The duration of exposure ranged from 10 min (16), 30 min (14), 3–24 hr (9,17,18), and up to several days (6). These variations make it quite futile to discern a pattern regarding the time of onset of anhidrosis, the period of peak effect and the rate of decay to a normal level of sweating. However, there is good agreement that sweat suppression persists for a comparatively long time, generally two to four weeks (6,17,19). The only divergent finding is that of Reller & Luedders (14). After establishing complete axillary anhidrosis, they could still show 30% sweat suppression after 20 days. Based on a mathematical model they suggest that complete restoration to the normal sweating state might take up to 78 days!

In view of the welter of conflicting findings we deemed it necessary to establish a more rigorously controlled model for appraising the kinetics of anhidrosis.

1. ONSET OF ANHIDROSIS

Method

200μl of a 20% aqueous solution of aluminum chloride hexahydrate, $AlCl_3 \cdot 6H_2O$, was pipetted into wide-rimmed aluminum chambers [a modification of Frosch & Kligman's (20) Duhring Chamber] containing two snugly fitting layers of nonwoven cotton cloth (Webril®, KENDALL, Boston, Mass.). The chambers were glued to the skin with a highly adherent adhesive (Duro-Tak® 30-1289, NATIONAL STARCH & CHEMICAL CO., Bridgewater, N.J.). The chambers were further secured by nonocclusive adhesive tape (Dermicel®, JOHNSON & JOHNSON, New Brunswick, N.J.). A set of six chambers was applied to both volar forearms of each of six subjects with an interval of 24 hr between applications on the right and left arms. The exposures on each arm were for 15 min, 1, 2, 3, 6, and 24 hr, layed down so that all could be removed at the same time. The treated sites were water-rinsed and blotted dry. Immediately after removing the second set, sweat suppression was estimated by thermal stress.

Results

The time pattern of sweat suppression is shown in Figure 1. It took about 60 min for an appreciable anhidrosis to develop. A few ducts were closed after 15 min. Sweat suppression reached 80% in about 6 hr and was invariably complete (100%) by 24 hr.

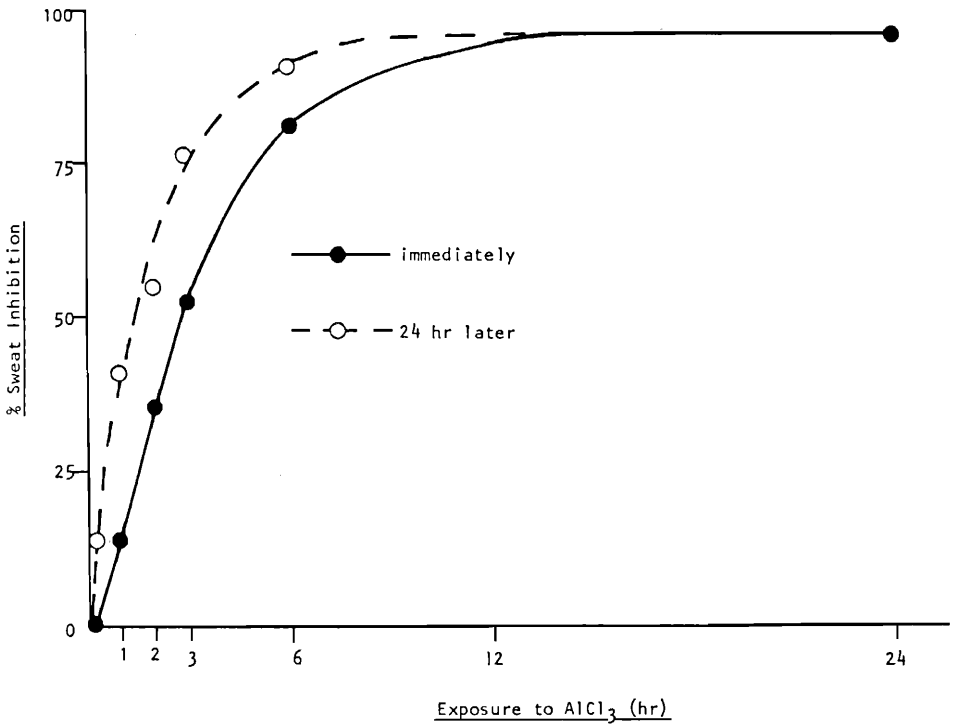

Figure 1. Development of sweat inhibition following occlusive application of 20% $AlCl_3 \cdot 6H_2O$. Suppression is considerably greater when thermal stress is delayed for 24 hr in comparison to immediately after each exposure.

This pattern is to be compared with the one obtained after a delay of 24 hr before thermal stress. This waiting period sharply intensified sweat suppression; a 3-hr exposure now resulted in 75% inhibition compared to about 50% before.

Comment

To obtain nearly complete anhidrosis required at least 6 hr. The ducts succumbed at vastly different rates. A few were already nonfunctional after 15 min, while others delivered sweat for more than 6 hr. It should be pointed out that the imprint method is an all or none phenomenon—either a droplet forms or it does not.

The results imply considerable heterogeneity among the sweat units. The size of the sweat pore is possibly the determinant factor. This is impossible to evaluate since the orifices are virtually invisible even with the powerful eye of the scanning electron microscope. Then, too, susceptibility might be expected to be inversely proportional to the rate of secretion.

The relatively slow onset of sweat inhibition and the augmentation of anhidrosis after a 24-hr wait suggest that some slowly evolving biological response has to be brought into play. We could not confirm the findings of Tronnier & Rentschler (16) or Reller & Luedders (14), who obtained a marked anhidrosis after short exposures of 10 and 30 min, respectively.

II. DURATION OF ANHIDROSIS

Method

A 20% aqueous solution of $AlCl_3 \cdot 6H_2O$ was applied by occlusive patches to the lower backs of 14 subjects for 24 hr. 5 cm squares of Webril saturated with the solution were sealed to the skin under overlapping strips of impermeable adhesive tape (Blenderm®, 3M COMPANY, St. Paul, Minn.).

In another group of 18 subjects, 20% $AlCl_3 \cdot 6H_2O$ was applied for 3 hr via the chamber on the forearms. In both groups, sweat suppression was estimated 1, 7, 14, and 21 days later.

Results

The solid anhidrosis induced by a 24-hr exposure was almost unchanged after seven days. After two weeks, some ducts had begun to deliver sweat. Thereafter an increasing number of units became competent. Complete restoration generally took three weeks. In a few cases some suppression was evident for almost a month.

This pattern of restoration was similar on the forearm sites exposed for 3 hr, but at a somewhat lower level owing to the lesser initial degree of anhidrosis. Here too, some units were still inactive by the end of three weeks (Figure 2).

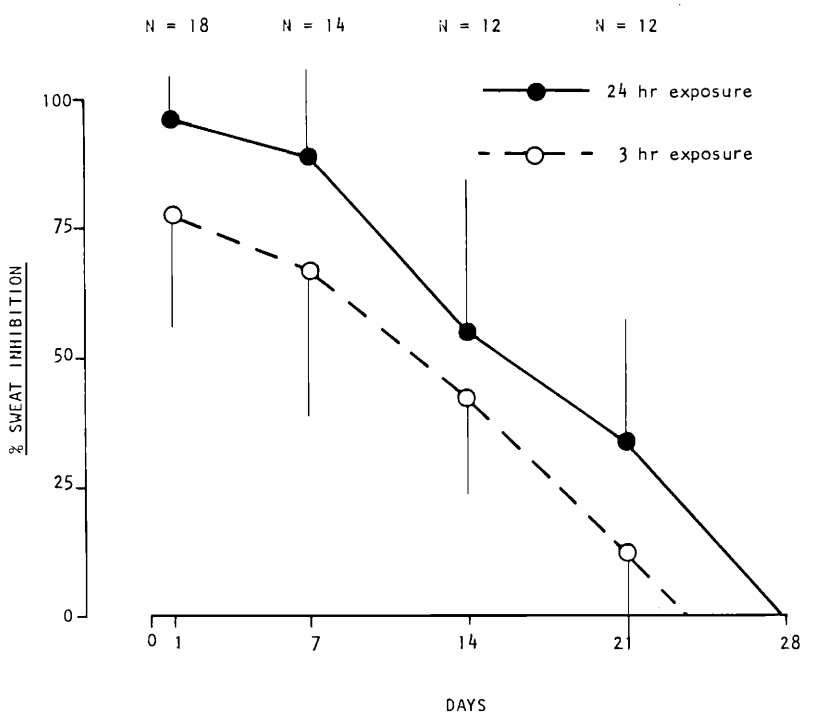

Figure 2. Duration of anhidrosis after occlusive application of $AlCl_3 \cdot 6H_2O$ for 3 and 24 hr. The longer exposure results in near complete anhidrosis, requiring about one month for sweating to return to the original level.

Comment

The long duration of anhidrosis is in general accord with the observations of previous investigators (6,17,19).

Assuming a physical block in the ducts, its removal is likely accomplished by the process of epidermopoiesis; the epidermis renews itself by constant proliferative activity. The time required to replace the stratum corneum on the forearm and back is about two weeks, while renewal of the whole epidermis takes about a month. Since suppression persisted for up to four weeks, the obstruction would have to extend through the entire intra-epidermal portion of the duct. This interpretation is concordant with the stripping experiments which will now be described.

STRIPPING

Papa & Kligman (21) distinguished "high-level blockade," induced by strong tissue reactants such as formaldehyde and trichloracetic acid, on the basis that Scotch-tape stripping would instantly relieve the anhidrosis. Histologic study showed a precipitate in the sweat pores. This high-level obstruction was demonstrated also for glutaraldehyde by Gordon & Maibach (22). By contrast, both pairs of workers failed to restore sweating by stripping aluminum treated sites. This implied a block below the level of the stratum corneum. The observations of Hunziker et al. (12) are not quite in agreement since stripping resulted in a variable pattern of sweat restoration. Accordingly, the matter was restudied with greater care.

Method

Anhidrosis was induced at four sites on the forearms of six volunteers by 3-hr chamber exposures to 20% $AlCl_3 \cdot 6H_2O$. One site was left as a control. A second was stripped to the glistening layer 24 hr after exposure as gently as possible (sharp stripping produces an exudative, inflammatory reaction which itself can interfere with sweating for some days). The third and fourth sites were stripped on the 7th and 14th day, respectively. In each instance sweat suppression was estimated immediately after stripping.

Results

The unstripped sites behaved as before with a slight decrease in anhidrosis at 7 days. Thereafter, sweating gradually increased and was restored to the original level by about three weeks.

Stripping one day after the exposure had no effect whatever in relieving the anhidrosis. However, the duration of anhidrosis was shortened. Seven days after the stripping, hypohidrosis was about 10% less than the control and by 14 days approximately 20% less. Though not great, these changes were consistent. The sites stripped 7 days after exposure were questionably affected, there being perhaps a 5% increase in the proportion of active units. Sites stripped 14 days after the exposure showed only a slight relief of sweat suppression.

Comment

Stripping performed a day after establishing anhidrosis did not result in sweating. No formerly closed ducts became patent. When stripping was delayed 7 to 14 days after

exposure, anhidrosis was lessened to only a modest degree. These facts argue strongly for a deep block. Moreover the obstruction clearly extends to different levels in individual ducts. Normally there is about a 50% recovery after two weeks. Stripping at that time did not open up new ducts indicating that the block was still below the level of the horny layer. The only effect of stripping was to lessen slightly the duration of anhidrosis. This is understandable since the trauma of stripping enhances epidermal turnover. By accelerating epidermopoiesis the block will be moved distally at a faster rate.

STUDIES OF MILIARIA

In their first paper, Shelley & Horvath (6) showed that aluminum chloride could produce miliaria crystallina. In their second work (7), they produced miliaria rubra. No explanation was given as to why the lesions took the form of miliaria crystallina in some instances and miliaria rubra in others.

Papa & Kligman (9) saw only *M. rubra,* while Reller & Luedders (14) produced both *M. rubra* and *M. profunda* with aluminum salts. These types of miliaria are related to obstruction at different levels, viz., *M. crystallina* within the horny layer, *M. rubra* in the epidermis and *M. profunda* in the dermis. All of these should appear in the same persons if the aluminum block extends to different levels as the recovery pattern and the stripping studies suggest.

METHOD

Anhidrosis was induced on the backs of 12 subjects by a 24-hr occlusive patch of 20% $AlCl_3 \cdot 6H_2O$. The subjects were heat-stressed at varying times thereafter. Small discrete wheals were interpreted to be *M. profunda,* tiny papules as *M. rubra* and dew-drop vesicles as *M. crystallina.* The latter were sometimes so diminutive as to be visible only with the aid of a magnifying glass. The degree of miliaria was graded on a 1 to 4 scale, depending upon the quantity of the lesions and not their individual size.

Results

Thermal stress regularly brought forth miliarial lesions in everyone, starting with the first heat stress 24 hr after exposure. We emphasize that the subjects sweated vigorously for at least 30 min in the hot box. At 24 hr, a mixture of *M. profunda* and *M. rubra* was present. About 75% of the obstructed ducts exhibited miliarial lesions. A week later, a few crystallina-type lesions were interspersed among *M. profunda* and *M. rubra.* The density of lesions was about as great as after 24 hr. At two weeks, when the anhidrosis was subsiding, *M. crystallina* and *M. rubra* lesions made up the display, with *M. profunda* becoming increasingly uncommon. By this time, about a quarter of the ducts showed miliaria. After 21 days, *M. profunda* had disappeared entirely and *M. rubra* lesions were decidedly a minor component; *M. crystallina* was the dominant type (Figure 3).

Comment

Miliaria is a regular concomitant of the anhidrotic state provided the heat stress is sufficient to provoke intense sweating. However not all obstructed ducts will rupture. Individuals differ greatly in this regard. The sequence of miliarial lesions following

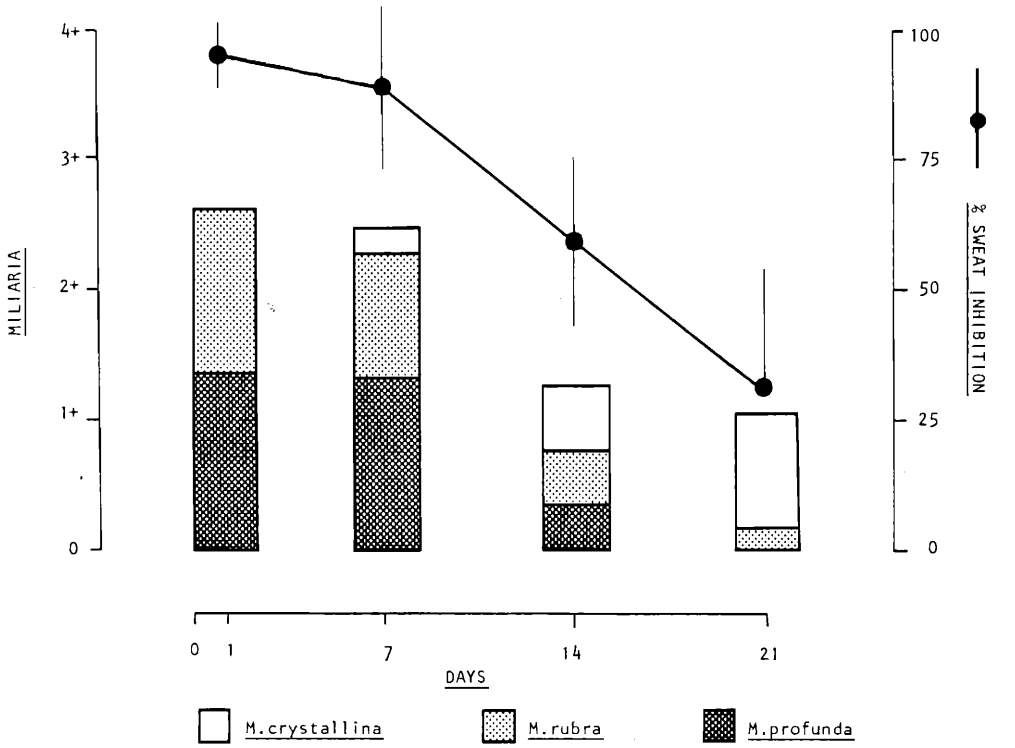

Figure 3. Type and intensity of miliaria during anhidrosis induced by 24-hr occlusive exposure to 20% $AlCl_3 \cdot 6H_2O$. Severity of the lesions parallels sweat suppression decreasing gradually with time. Early on *M. rubra* and *M. profunda* predominate. *M. crystallina* becomes common after two weeks and is overwhelmingly dominant by three.

aluminum anhidrosis could have been predicted. For the first week, the lesions were a mixture of *M. rubra* and *M. profunda*. By two weeks, *M. profunda* was on the wane and *M. crystallina* had become prominent. By three weeks, there was only one response, *M. crystallina*.

This sequence is easily explained. The obstruction starts at a deep level and becomes progressively shallower, until it is located entirely within the horny layer. The early obstruction must extend into the dermis in order for the wheal-like *M. profunda* lesions to develop. These resorb in a matter of minutes when sweating stops. A block within the intra-epidermal portion of the acrosyringium is the precondition for the development of *M. rubra*. That both occur together in the early phase bears out what was already disclosed by the study of the duration of anhidrosis, viz., different ducts are blocked at different levels. It is logical, indeed inevitable, that the final lesion in the sequence be *M. crystallina,* reflecting a superficial intra-corneal block. The progressive transformation of the initial deep block to an ever more superficial location is attributable to epidermopoiesis.

It is appropriate to note here that a somewhat similar sequence of miliarial lesions was observed when anhidrosis was induced by occlusive patches for 3 to 4 days. This results in the formation of an obstructing agglomerate of degenerating leukocytes and PAS-positive masses within the lumen of the sweat ducts (8).

HISTOLOGIC EXAMINATION

The observations presented so far clearly implicate a physical block of some sort. But, with one exception, various observers have failed to visualize the obstruction. Reller & Luedders (14) found casts which took a reddish color with the aluminum stain. The cast was mainly within the "distal segment of the epidermal sweat duct," a finding somewhat incompatible with the long duration of the anhidrosis. However, they did occasionally find aluminum-staining material well below the epidermis.

Method

Anhidrosis was induced on the back of 16 subjects by either 3- or 24-hr occlusive patches of 20% $AlCl_3 \cdot 6H_2O$. Full thickness specimens were excised shortly after the exposure or 7 days later. Prior to removal of the biopsies a short thermal sweat stimulus was given to verify that the site was anhidrotic. After formalin fixation serial 6 μm sections were cut and stained with H&E, PAS and the morin technique. With the latter, aluminum-containing material fluoresces brightly.

Results

After a 3-hour exposure and even more so after 24, an eosinophilic, amorphous cast was found within the lumen throughout the entire acrosyringium. The luminal cells of the intra-epidermal portion showed moderate toxic changes indicated by pyknotic nuclei and eosinophilic cytoplasm (Figure 4). The luminal masses were PAS-positive and diastase-resistant. The casts were vividly visualized by the fluorescent morin technique (Figure 5). Moreover, they could be shown to extend well into the dermal segments, sometimes occupying the ducts right down to the secretory coil. By contrast, the intra-corneal portion of the ducts was patent with only a thin layer of aluminum-containing material coating the keratinized cells (Figure 6).

In all cases, a modest infiltrate of lymphocytes surrounded the ducts at about the level where these entered the epidermis. The histologic picture was consistent with a sub-clinical miliaria. We emphasize that this change was provoked by the thermal stress which preceded taking the biopsy. The periductal infiltrate did not occur when tissue was removed without prior sweating. Hence, inflammatory changes are not an intrinsic feature of aluminum anhidrosis.

After a week, a somewhat different view greeted the eye. The damaged and now shrunken luminal cells had sloughed into the lumen, enveloping the amorphous material which was still strongly PAS-positive. This agglomerate extended throughout the acrosyringigum including now the stratum corneum (Figure 7). The mid-dermal ducts were patent. Occasionally, intra-corneal microvesicles typical of *M. crystallina* were observed.

We note here in passing that aluminum chlorhydroxide, the partially neutralized salt of aluminum chloride, produced the same histologic changes but to a lesser degree.

Comment

Though most brilliantly visualized by the fluorescent morin technique, the casts were observed in both PAS and H&E stained specimens. It is utterly beyond our understanding how a brigade of investigators, including ourselves, had failed to see these.

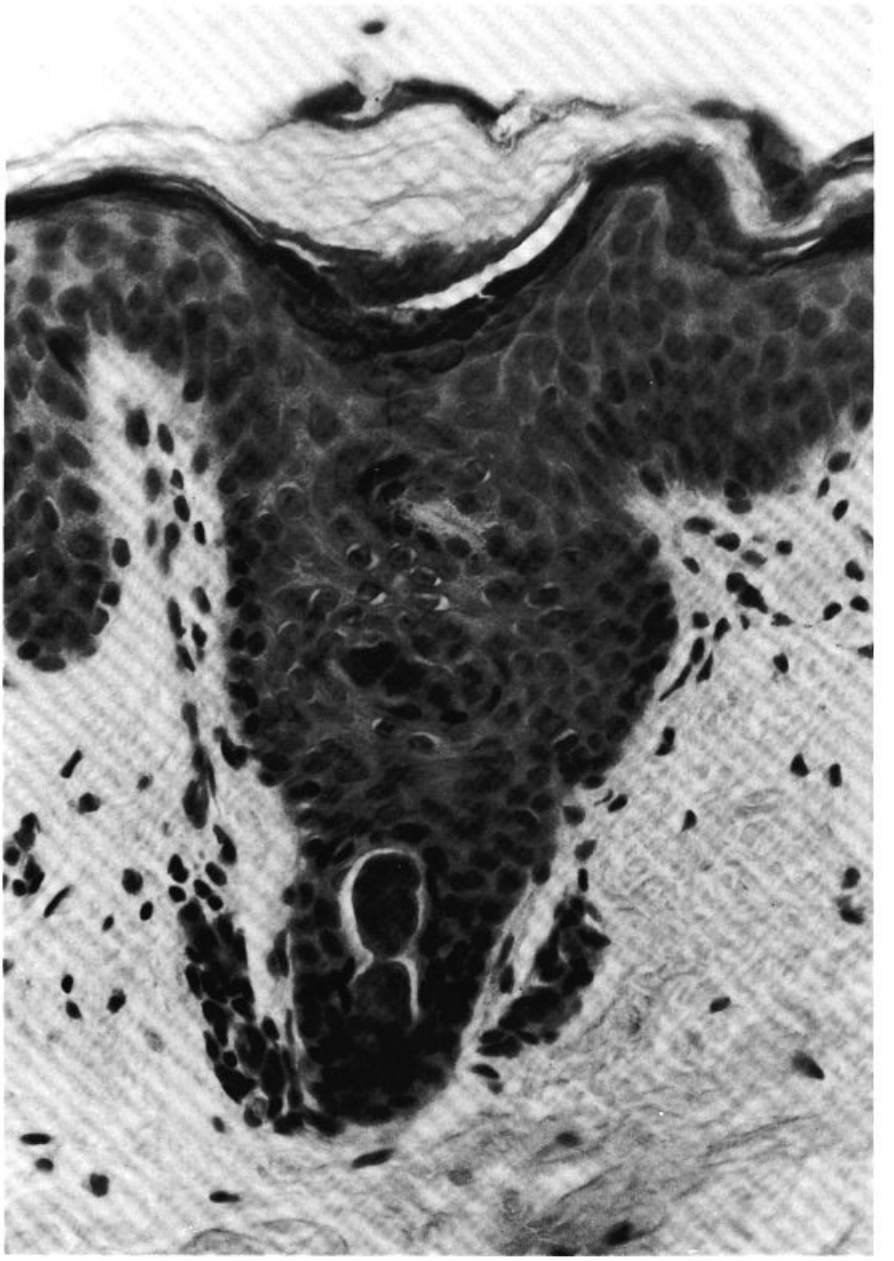

Figure 4. The acrosyringium immediately after a 3-hr exposure to 20% $AlCl_3 \cdot 6H_2O$. An amorphous cast has formed within the intraepidermal portion of the duct exempting the horny layer portion. Below the level of the granular layer the luminal cells are shrunken with pyknotic nuclei. A mild lymphocytic infiltrate surrounds the duct where it enters the epidermis. The latter change is not an intrinisic part of the process, representing sub-clinical miliaria after heat stress (H&E, ×400).

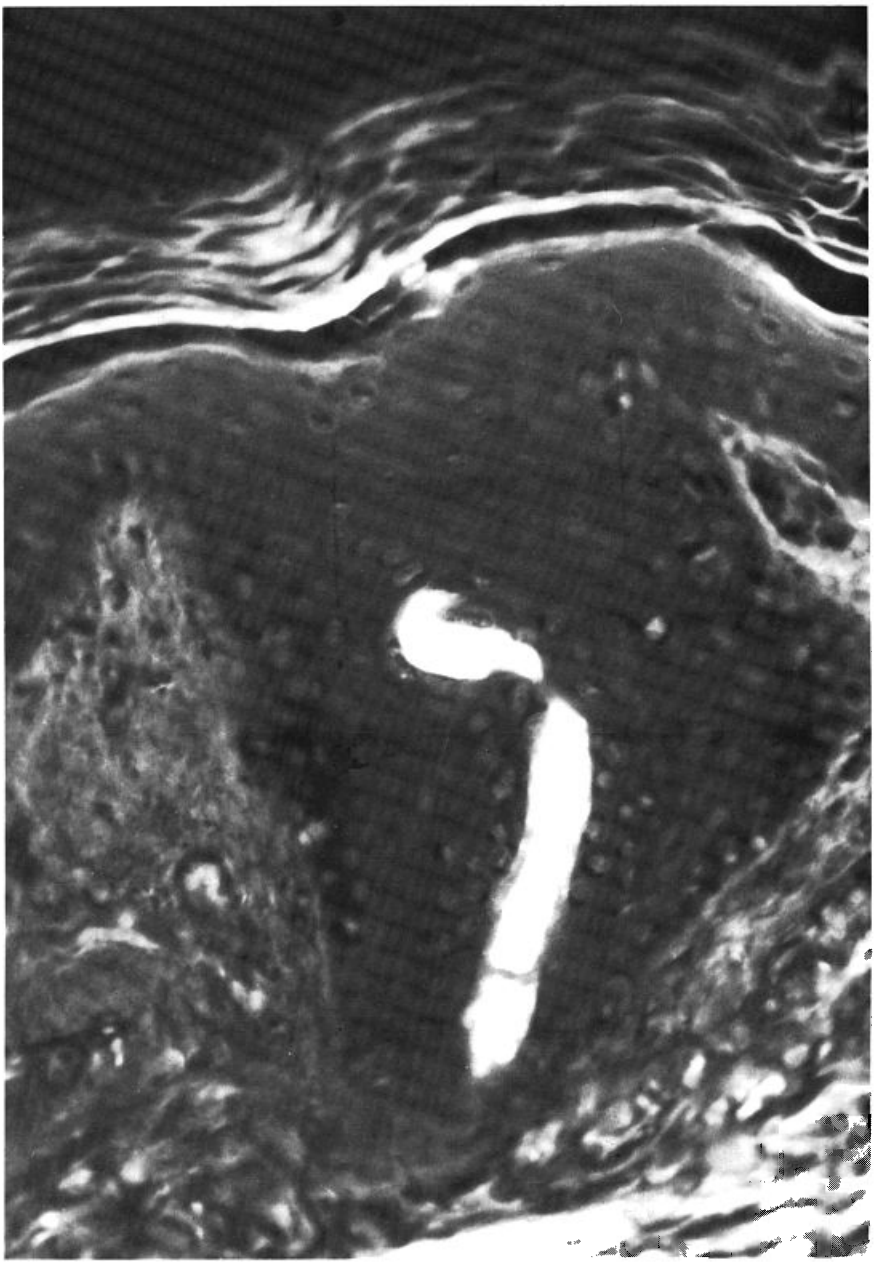

Figure 5. After exposure to 20% $AlCl_3 \cdot 6H_2O$ for 24 hr, the intraepidermal portion of the duct contains a solid mass of aluminum-positive material corresponding to the eosinophilic, amorphous cast with the H&E stain (Morin, ×400).

Our findings establish beyond further doubt that there is a physical obstruction to the passage of sweat. Moreover, we now have sufficient anatomic and physiologic information to fashion a coherent concept of how aluminum chloride, and presumably other aluminum salts induce the anhidrotic state.

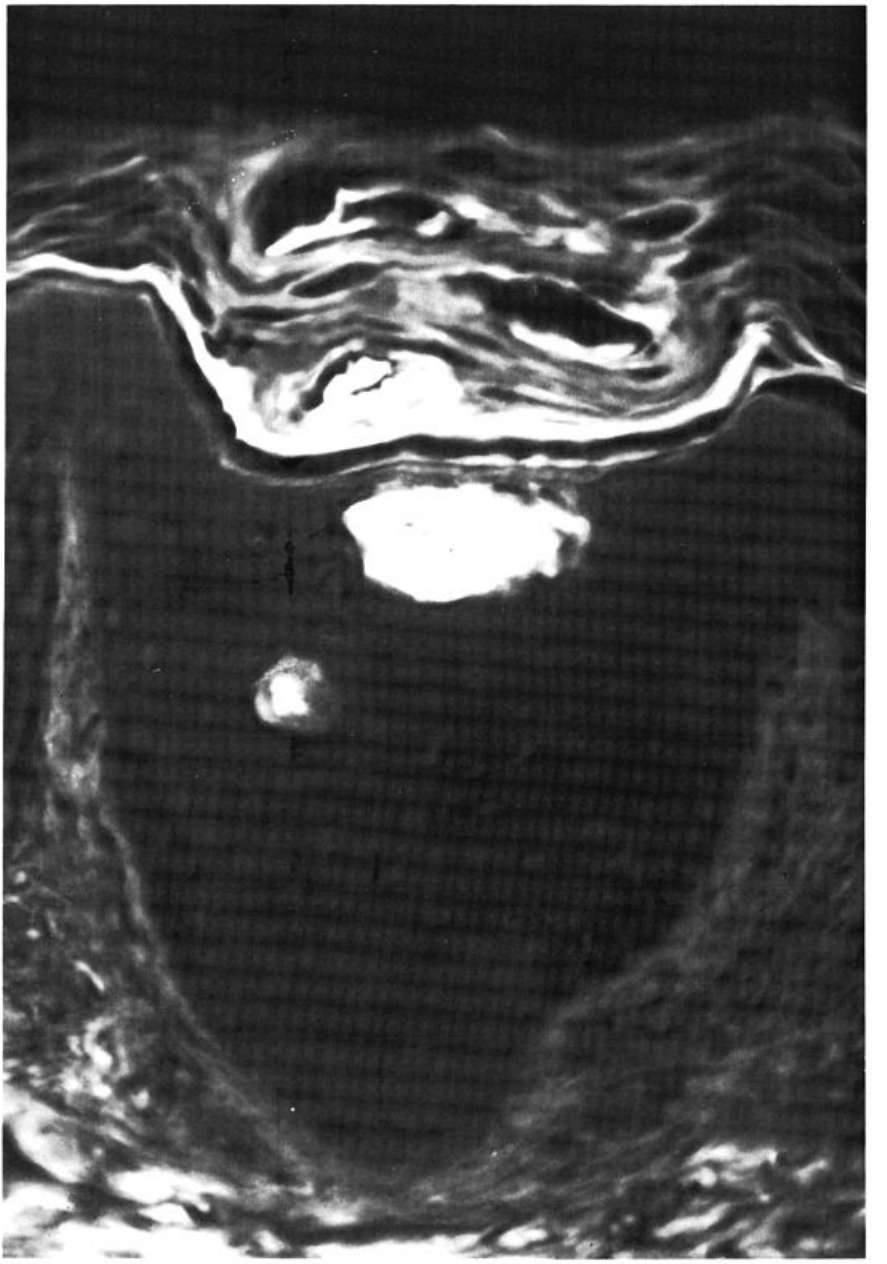

Figure 6. Morin stain for aluminum after a 24-hr exposure to 20% $AlCl_3 \cdot 6H_2O$. Fluorescent material coats the patent duct in its intracorneal portion. Further down, within the viable portion of the epidermis, the duct contains a solid mass of fluorescent material (Morin, ×400).

At first the casts are deeply situated, sometimes extending down to the secretory coil. Sometimes they were limited to the acrosyringium. Their depth was variable from duct to duct of the same subject. This explains why some ducts become patent in two weeks and others not until four.

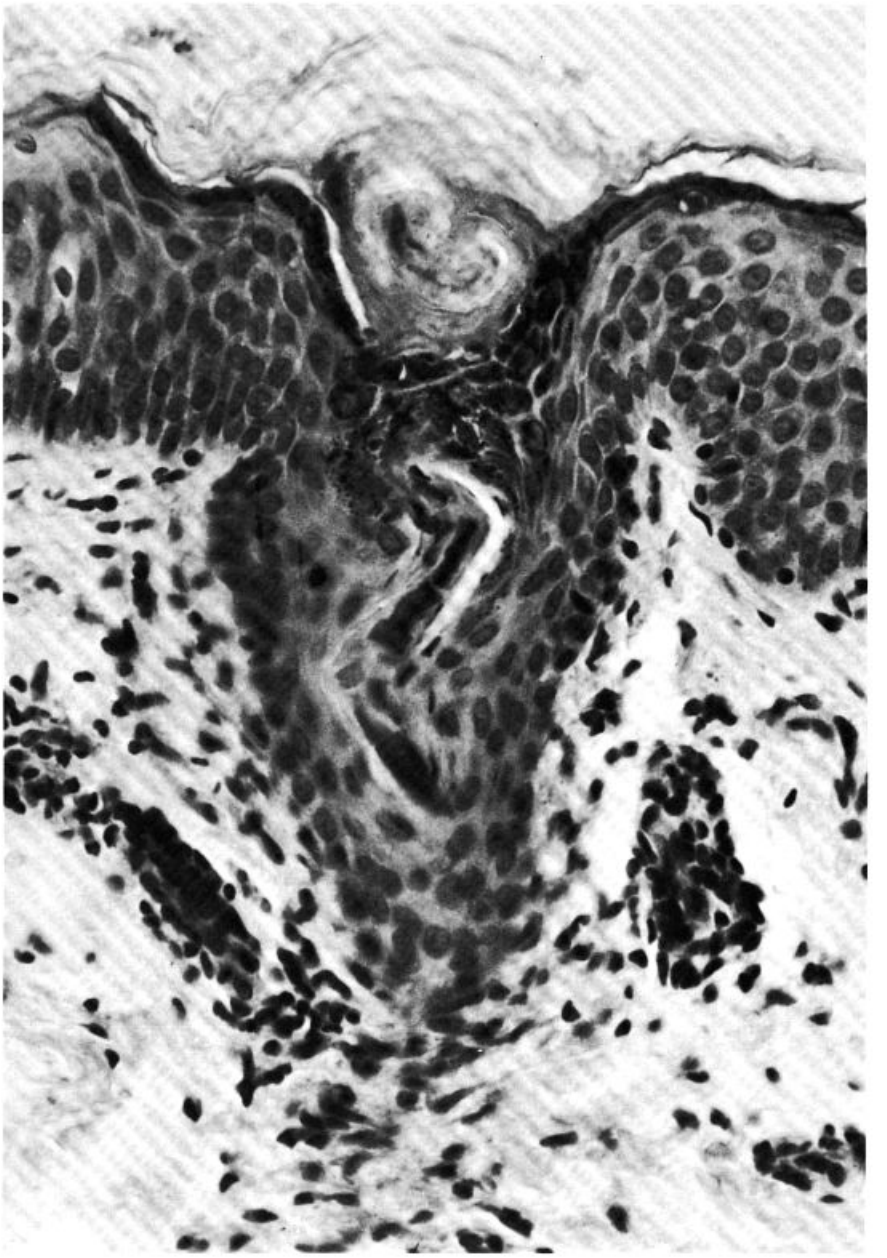

Figure 7. One week after a 24-hr exposure to 20% $AlCl_3 \cdot 6H_2O$. A solid cast extends throughout the epidermal portion of the duct including the horny layer. Necrotic luminal cells have sloughed into the duct enveloping the cast. The usual sub-clinical peri-ductal reaction due to sweat retention is present (H&E, ×400).

Under these circumstances Scotch-tape stripping would not be expected to restore sweating. The block is well below the horny layer. The fact that the luminal cells are damaged at the onset is a matter of no little importance. These cells subsequently die and slough into the lumen. Whereas Reller & Luedders (14) propose that the cast is a

polymeric gel formed by a simple chemical reaction between the acidic salt and the less acidic sweat, we postulate that the obstructive material derives in part from the cells. One possibility is that aluminum reacts with the so-called glyco-calyx; the latter forms a mucilage-like covering on the outer surface of epidermal cells. This aluminum-polysaccharide complex might be the source of the cast. Toxic effects to cell membranes could also allow internal contents to diffuse into the ducts and contribute to the mass. It is important to note that the amorphous cast is PAS-positive, indicative of the presence of neutral muco-polysaccharides. We shall mention here that non-aluminum metallic antiperspirants also result in PAS-positive casts, suggesting a biologic product not merely a reaction between aluminum and sweat. This will be the subject of a later communication.

It is noteworthy that the earliest obstruction exempts the intracorneal coils of the sweat duct. Here the luminal cells are fully keratinized with thickened cell membranes which are presumably resistant to the damaging effect of aluminum. The cast forms below the horny layer where the cells are viable. It will be recalled that Blank et al. (23) showed that aluminum chloride could not cross the horny layer barrier into the dermis. Moreover, aluminum chloride forms complexes with keratinized tissue (24), further limiting its diffusion. We would emphasize that damage to cells is an important feature of the events leading to anhidrosis. In this regard Lansdown (25) found a correlation between antiperspirant activity and the ability of aluminum salts to cause irritation in mouse, rabbit and pig skin.

It is also worth emphasizing that the histopathologic picture is distinctive from anhidrosis produced by all other means except by other metallic salts. The latter will be discussed in a future work. Unlike prolonged occlusion, which provokes an inflammatory response with dense invasion of the acrosyringium by leukocytes, the aluminum effect is completely non-inflammatory. The micro-miliaria which we observed was provoked by sweating just prior to biopsy and is a secondary event.

Another distincitive factor of aluminum anhidrosis is an inconsistent intensification of the methylene blue pore pattern, previously noted by Papa & Kligman (9) and verified herein. The blue punctae which result from the iontophoretic application of the dye represent supravital staining of epidermal cells surrounding the viable portion of the acrosyringium (26). Immediately after induction of aluminum anhidrosis, some dyed spots were very much larger than others. This reflects increased diffusion across the epithelial lining and is consistent with the view of chemical damage to the lining cells. While the cast obstructs sweat delivery it is evidently partially permeable to methylene blue.

DISCUSSION

The sweat ducts are low-resistance pathways for the diffusion of water-soluble electrolytes. It is to be expected, therefore, that metallic salts will readily enter the ducts and percolate downwards. It is surprising that proof of the presence of aluminum within the ducts was so long in coming. In the foot-pads of rats Lansdown (27), using the morin stain, was able to show aluminum only on the surface and slightly in the pores.

Our work supports Reller & Luedder's claim that a physically demonstrable obstruction accounts for the anhidrosis induced by aluminum chloride. However, their interpretation of the nature of the obstruction and certain of their observations differ from ours. Hence, a detailed analysis seems justified.

They found reddish-staining aluminum masses, "predominantly in the distal segment of the epidermal sweat duct." In our specimens, aluminum chloride practically always reached the upper- and mid-dermis. Our method of application was doubtless more intense. At one week, they observed a separation of the entire duct from the surrounding epidermal tissue and regarded this as a "delayed" effect of aluminum. This total sloughing of the acrosyringium cannot be reconciled with our findings. In contrast, we saw damage in the luminal cells at the very outset; these soon died and sloughed into the lumen but the acrosyringium itself was never cast off. Perhaps Reller & Luedders were looking at an artifact of histologic processing. We believe we have examined many more biopsies.

At three weeks, Reller & Luedders found that ducts were dilated and separating as hypertrophied, distorted acrosyringical units. These late alterations were never observed in our material. Indeed, most of the changes had regressed.

We hold a different view concerning the nature of the aluminum-containing material within the ducts. Our notions too are purely speculative. Reller & Luedders studied a number of antiperspirant metallic salts and created the "emphraxis" theory. According to this view, the salts form polymeric gelatinous hydroxide precipitates at or below physiologic pH. It is the gel itself which constitutes the obstruction. We neutralized aluminum chloride with sodium hydroxide and stained the resultant flocculant with PAS. In contrast to the in vivo situation, the flocculant was PAS-negative. The model used by Reller & Luedders to demonstrate hydroxide gels is a far cry from physiologic conditions. They first measured the flow of water through a millipore filter in a Swinny holder under a fixed pressure of 32 cm Hg. Then they immersed the filter in the metallic solution and suspended it over ammonium hydroxide, thereby assuring complete neutralization by ammonia vapor. The percentage reduction in flow was taken as a measure of gel formation. However, in real life complete neutralization is impossible. The pH of sweat is 5.5 to 6.0. With sodium hydroxide we found incipient precipitation of aluminum chloride at this pH and none when aluminum chloride was added to sweat itself. We see the obstruction as more than a reaction product of sweat and the antiperspirant. Tissue components contribute. It is noteworthy that the anhidrosis gradually deepens over a 24-hr period, suggesting a biologic reaction.

Finally, the perspicacious observer will note that our report makes no mention of the keratotic and parakeratotic plugs which earlier workers had imagined to be the cause of the block. Why did we fail to see them? It will be recalled that plugs result from repair of ducts damaged by bouts of miliaria. Our focus was on the early events associated with anhidrosis and not the late stages of repair after rupture of the ducts.

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