

## EXPERIMENTAL MILIARIA IN MAN

### I. PRODUCTION OF SWEAT RETENTION ANIDROSIS AND VESICLES BY MEANS OF IONTOPHORESIS\*†

WALTER B. SHELLEY, M.D., PETER N. HORVATH, M.D., FRED D. WEIDMAN, M.D., AND DONALD M. PILLSBURY, M.D.

Sweat retention due to obstruction of the sweat duct in the presence of functioning glandular acini plays a primary role in miliaria crystallina (1, 2) miliaria rubra (3, 4) tropical anidrosis (4, 5, 6) Fox-Fordyce disease (7), and hidrocystoma (8, 9). In addition, sweat duct obstruction may occur secondarily in ichthyosis, atopic dermatitis and in seborrheic dermatitis (10). It might be expected to occur in granulosis rubra nasi, certain types of chronic vesicular eruption of the palms and soles, contact dermatitis, and acro-dynia. The effect of many popular local anidrotics is achieved through the production of a closure of the sweat duct orifice (11). With the recent clear definition of the sweat blockage factor (10) there has come a need for further studies on the pathogenesis which attends primary closure of the excretory channel of the sweat gland.

Many theories have been advanced as to the etiology of this functional obstruction. In the case of miliaria, Haight (12) suggested that a simple mechanical closure of the spiraling intraepidermal duct resulted from the pressure of an excessive volume of sweat. Pollitzer (12) explained the closure as due to an abnormal increase in the imbibition of sweat by the stratum corneum, with resultant blockage at the duct orifice by these enlarged cells. He reasoned that this degree of imbibition occurred, when excessive lipid had been lost from the skin surface. To support his hypothesis, he pointed out that the rarity of miliaria on the face could result from the fact that the face is richly supplied with sebum. Sulzberger (3) advanced the hypothesis that profuse sweating leads to maceration of the skin surface, faulty keratinization, occlusion of sweat pores by horny plugs, and the subsequent appearance of miliaria. O'Brien (4) regards miliaria rubra as a manifestation of lipid deficiency of the skin. He states that this deficiency results from too rapid a removal of sebum by clothing, soap, powder, lotions and alcohol, or by a diminution in the production of sebum. To test his theory, he subjected 20 individuals to artificial lipid depletion by applying fat solvents. In 15 of the subjects, a dermatitis appeared which resembled miliaria rubra both clinically and histopathologically. Unfortunately, no details of the method were given. This, however, is the solitary report of an experimental production of miliaria.

\* From the Department of Dermatology and Syphilology, School of Medicine, and Graduate School of Medicine (Dr. Donald M. Pillsbury, Director), University of Pennsylvania Philadelphia.

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Lobitz (13) described a patient with generalized miliaria in whom a vitamin A disturbance was present as manifested by a flat vitamin A tolerance test and clinical night blindness. Milenkow (14) reported a patient with pellagra in whom a biopsy disclosed small cylindrical masses obstructing the lumina of the sweat glands. A third observation on the relationship of plugging of the sweat duct to vitamin intake was made by Davidson *et al.* (15). They noted sweat retention vesicles in prisoners of war on a starvation diet.

Experimental studies on the production of sweat retention have been limited to O'Brien's incidental note mentioned above, and to a report by Schidachi (16), who produced hidrocystoma experimentally in cats by surgical removal and reattachment of the upper layers of the skin, thus producing blind sweat ducts.

TABLE 1

*Methods producing experimental sweat retention anidrosis and vesicle formation in heat*

- 
1. Electrical-iontophoresis
  2. Heat
  3. Cold
  4. Ultraviolet light
  5. Chemical
    - Aluminum chloride
    - Soap\*
    - Turpentine
    - Phenol
  6. Adhesive tape
  7. Wet dressing (water)
- 

\*Sweat retention without vesicles.

Our experiments have been conducted on the skin of normal human volunteers to determine methods of producing sweat gland obstructions. It was found that certain measures which cause epidermal injury invariably produced blockage of the sweat duct orifices, with the consequent production of localized sweat retention anidrosis and vesicles. Such an effect was not specifically related to the action of a single injurious process, but as is seen in Table 1, occurred following injury ranging from that due to iontophoresis to that due to simple maceration from wet dressing. The iontophoretic method was selected for primary analysis because it permitted standardization of injury.

It was found possible to produce experimental anidrosis and miliaria crystallina type vesicles in man consistently by means of iontophoresis, due to closure of the sweat duct with retention of sweat within the duct. The details of action of the other methods of producing experimental anidrosis and sweat retention vesicles (Table 1) are under evaluation at present, and will be reported upon in a subsequent paper.

#### METHOD

Thirty-five normal healthy male subjects were studied, employing both standard commercial, and specially constructed iontophoresis units. A 45 volt ap-

paratus<sup>1</sup> permitting 5 channel circuits (17) served in most of the work. Electrodes consisted of equally weighted (400 grams) stainless steel plates, 2 cm. square, which rested on the skin with 4 layers of moistened filter paper interposed. Current densities applied at the active electrode varied from  $\frac{1}{8}$  ma/cm<sup>2</sup> to  $1\frac{1}{2}$  ma/cm<sup>2</sup>. Aqueous solutions of various compounds were used under the active electrode, whereas a padded indifferent electrode was soaked in a saline solution. The areas of skin treated were not washed with soap during the test periods. Other than this no special measures were taken regarding the skin.

The effect of the iontophoresis treatment on the function of the sweat gland apparatus was determined in the following way. For purposes of stimulating sweat secretion the subjects were placed in a thermal cabinet. This was a chamber 8' x 4' x 4' in which the nude subject rested on a bed. Six infrared lamps<sup>2</sup> in two parallel banks 24" above the bed level provided radiant heat stimulus. Visible sweating generally resulted after 5 to 10 minutes of exposure, and became profuse as the humidity of the cabinet increased. A blower type exhaust fan provided ventilation. Graduated degrees of heat were secured by varying the number of lamps. Sweating was graded by means of the Guttman (18) quinizarin dye technic. Quinizarin is a dye which changes from a brick red color to a deep purple in the presence of water. The dye was dusted on the skin with cotton, or sprayed with a small atomizer after being mixed with starch and sodium carbonate in the following formula:

|                       | <i>Grams</i> |
|-----------------------|--------------|
| Quinizarin.....       | 35           |
| Sodium carbonate..... | 30           |
| Starch.....           | 60           |

Preceding application of a liquid vehicle on the skin was found unnecessary. Degrees of sweating are recorded as:

- 0 = no color change: no visible sweating
- 1+ = a few small purple dots
- 2+ = less than 50% of surface area dye changed to purple
- 3+ = more than 50% of surface area dye changed to purple
- 4+ = purple over entire area.

Grading was not done until control areas showed 4+ sweating. For the purposes of this experiment the quinizarin method was considered superior to the starch-iodine reaction since painting the skin repeatedly with iodine might be expected to produce epidermal injury in certain subjects.

Biopsies were taken on 8 of the subjects, after a 30 minute period of sweating, at varying periods of time after treatment by iontophoresis. Each of these was serially sectioned and stained with hematoxylin and eosin.

Special observations were made on the surface of the skin under a dissecting microscope and, in addition, auxiliary physiological technics were employed which will be detailed under the section on results.

<sup>1</sup> Assistance of Smith, Kline and French Laboratories in the construction of this apparatus is acknowledged.

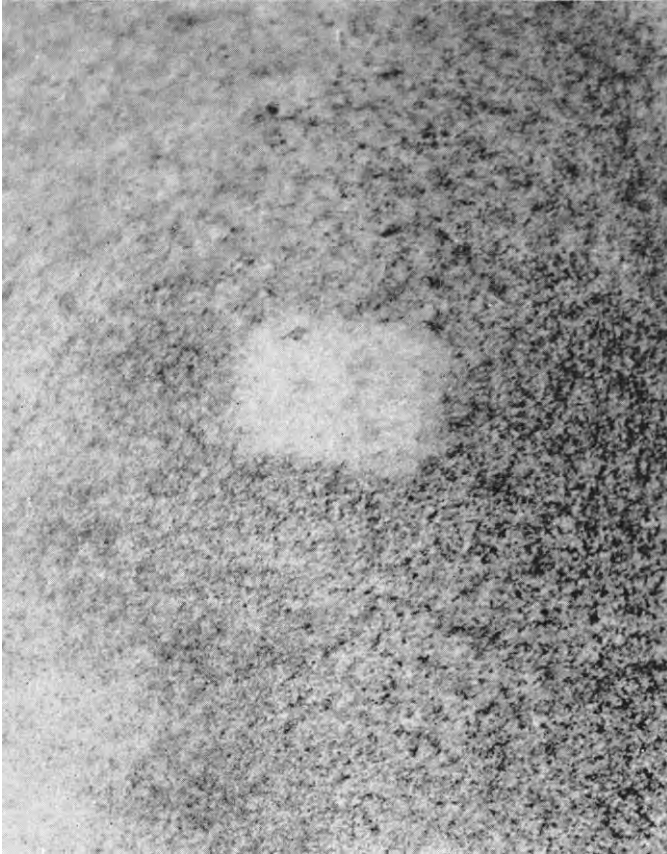
<sup>2</sup> General Electric Infrared Reflector lamps, 250 watts.

The majority of these studies were made in the winter, so that appreciable sweating occurred only when the subjects were tested in the heat cabinet.

#### RESULTS

##### *A. General*

In the non-sweating subject the local areas treated with iontophoresis showed either no change or a slight patchy brownish discoloration which appeared within 48 hours. Other than the color changes and an initial transitory urticaria,



PHOTOGRAPH NO. 1. Post-iontophoretic area of anidrosis. Subject had been treated 5 days previously with an iontophoretic current density of 1 ma/cm<sup>2</sup> for 10 minutes, using distilled water under the anode. Prior to photography and spraying with quinizarin subject had been in the heat cabinet for 10 minutes. The treated area shows anidrosis, and the surrounding darkened area shows normal sweating.

which were associated with use of higher current densities, the skin was unchanged. Rarely a small punctate iontophoretic burn was induced due to irregular current flow. After 2 to 3 weeks a transitory branny desquamation was noted. Following this, the skin became entirely normal.

In the sweating subject, a marked difference appeared between the treated and



PHOTOGRAPH No. 2. Sweat retention vesicles 2  $\times$ . This is the area shown in Photograph No. 1, after subject had been sweating for 30 minutes. Dark spots are freckles.

untreated areas. No symptoms were noted but in the treated areas partial to complete anidrosis<sup>3</sup> (Photograph No. 1) with or without vesicles and bullae, was found. The number of vesicles (Photograph No. 2) varied from an occasional

<sup>3</sup> Anidrosis refers, in this report, to the absence of sweat on the skin surface.

one to a thick stippling of the entire surface. The vesicles were seen in all sizes, at times having an inflammatory areola. The anidrosis and vesicles generally appeared after a latent period of from 1 to 3 days in which sweating was normal and no vesicles could be produced. Vesicles disappeared several hours after sweating and could be made to reappear as often as desired by simply having the subject resume sweating. After 2 to 3 weeks, the sweating returned to normal and vesicles could not be made to appear, coincident with a fine desquamation. The entire cycle was complete in two to four weeks, depending upon the rate of desquamation. No sequelae of anidrosis were noted, such as followed miliaria in the tropics (4).

No method was at hand for stimulating the sebaceous glands so that effects on the orifice of the gland were difficult to ascertain. However, milia were not noted in the areas treated. Similarly, hair growth appeared to be normal. Percutaneous absorption of histamine through treated skin was normal as well as the vascular response to histamine.

### *B. Effect of certain selected factors*

With this initial information at hand an investigation was made of the effect of the following factors:

1. *Electrode characteristics:* (a) Polarity. The phenomena were produced only under the anode. In 10 different subjects the areas treated under the cathode were normal when distilled water or saline solution was used. In these subjects a current density of 0.5 ma/cm<sup>2</sup> was applied for 10 minutes.

(b) Composition. The use of electrodes made of Wood's metal, copper or steel gave the same result. The interchange of cotton, filter paper, blotter, or cloth under the electrode was likewise without influence.

(c) Size. This was varied within reasonable limits without effect. However, foot baths or large electrodes were not tested.

(d) Pressure. Varying the pressure on the electrode, manually, apparently caused no difference in reaction.

2. *Current density:* The milliamperage was a factor of prime importance (Table 4) Increasing it increased the effect; with the time constant, a graduated series of localized responses ensued in the subject stimulated to sweat in the following sequence: no effect, partial anidrosis, complete anidrosis, complete anidrosis with vesicles, and complete anidrosis with bullae. Moreover, increasing current density lead to shortening of the latent period which preceded these changes. It also increased the duration of anidrosis.

3. *Time:* The duration of treatment was comparable in importance to the current-density factor (Table 2). Increasing the time over which iontophoresis was applied increased the magnitude and duration of effect as well as reducing the latent period. Thus it was possible with an iontophoretic current of  $\frac{1}{8}$  ma/cm<sup>2</sup> applied for 30 minutes to produce anidrosis which corresponded to that seen following the application of  $\frac{1}{2}$  ma/cm<sup>2</sup> for five minutes.

4. *Compounds applied at anode:* Table 5 indicates 12 compounds used in determining what chemical or type of agent was most effective in producing anidro-

sis. It will be seen that distilled water is an effective as any of the preparations used. A further study on 4 subjects revealed the increased effect resulting from the use of distilled water.

TABLE 2

*Time curve of the effect of variable doses of iontophoresis on skin of one subject*

| AREAS | IONTOPHORESIS CURRENT |             | POST-TREATMENT TIME                        |        |         |         |        |        |        |        |         |         |
|-------|-----------------------|-------------|--|--------|---------|---------|--------|--------|--------|--------|---------|---------|
|       | Mc/Cm <sup>2</sup>    | Time        | 30 min.                                    | 6 hrs. | 24 hrs. | 36 hrs. | 2 days | 3 days | 6 days | 9 days | 14 days | 21 days |
|       |                       |             | Sweating response and presence of vesicles |        |         |         |        |        |        |        |         |         |
|       |                       | <i>min.</i> |  |        |         |         |        |        |        |        |         |         |
| 1     | 0.25                  | 5           | 4  | 4      | 4       | 4       | 4      | 4      | 4      | 3      | 4       | 4       |
| 2     | 0.25                  | 10          | 4  | 4      | 4       | 4       | 4      | 4      | 4      | 2      | 4       | 4       |
| 3     | 0.5                   | 5           | 4  | 4      | 4       | 4       | 3      | 4      | 3      | 3(v)   | 4       | 4       |
| 4     | 0.5                   | 10          | 4  | 4      | 4       | 4       | 4      | 4      | 2(v)   | 1(v)   | 2(v)    | 4       |
| 5     | 0.5                   | 15          | 2  | 2      | 2       | 2       | 1(v)   | 1(v)   | 1(v)   | 1(v)   | 1(v)    | 4       |

Treatment: active electrode = anode.  
 solution = distilled water.  
 area = back of subject.  
 subject No. 17

Grading of sweating: 0 to 4 plus, 0 being complete anidrosis.  
 (v) = presence of vesicles in treated area.

Experiments were repeated in duplicate on this subject with good agreement of results.

TABLE 3

*Variation between individuals in response to iontophoresis*

| SUBJECT | DAYS POST TREATMENT                        |      |      |      |    |
|---------|--|------|------|------|----|
|         | 2  | 5    | 9    | 14   | 21 |
|         | Sweating response and presence of vesicles |      |      |      |    |
| No. 11  | 3  | 4    | 4(v) | 4    | 4  |
| No. 12  | 0(v)                                       | 1(v) | 1(v) | 3(v) | 4  |
| No. 13  | 0(v)                                       | 0(v) | 3(v) | 3(v) | 4  |
| No. 14  | 0  | 0(v) | 4(v) | 4    | 4  |
| No. 15  | 0(v)                                       | 0(v) | 1(v) | 2(v) | 4  |

Sweating graded on 0 to 4 + scale, 0 being complete anidrosis.

(v) = presence of vesicles.

Factors: Area = back.

Current density 0.5 ma/cm<sup>2</sup>.

Duration of treatment = 10 minutes.

Electrode = anode -- distilled water.

5. *Individual variation:* Examples of interindividual variation are reported in Tables 3 and 5. Fair, blonde individuals were more affected than dark skinned subjects. Moreover, vesicle formation appeared to be retarded in men with low sweat rates. In one subject it was possible to increase the size and number

TABLE 4

Example of time curve of effect of variations in one subject of current density, solution at anode and duration of iontophoretic treatment

| CURRENT                 |                    |             | DAYS POST TREATMENT               |   |      |      |      |    |    |
|-------------------------|--------------------|-------------|-----------------------------------|---|------|------|------|----|----|
| Area                    | Ma/Cm <sup>2</sup> | Time        | 0                                 | 1 | 2    | 4    | 8    | 11 | 17 |
|                         |                    |             | Sweating and presence of vesicles |   |      |      |      |    |    |
| A. Distilled water      |                    |             |                                   |   |      |      |      |    |    |
|                         |                    | <i>min.</i> |                                   |   |      |      |      |    |    |
| 1                       | 0.12               | 5           | 4                                 | 4 | 3    | 2    | 2    | 2  | 4  |
| 2                       | 0.25               | 5           | 4                                 | 2 | 2    | 2    | 1    | 2  | 4  |
| 3                       | 0.50               | 5           | 4                                 | 1 | 2    | 2    | 1    | 2  | 4  |
| 4                       | 1.0                | 5           | 3                                 | 0 | 2    | 2(v) | 0(v) | 2  | 4  |
| 5                       | 1.5                | 5           | 1                                 | 0 | 0    | 1(v) | 1(v) | 3  | 4  |
| 6                       | 0.5                | 0.5         | 4                                 | 4 | 4    | 4    | 2    | 4  | 4  |
| 7                       | 0.5                | 1           | 4                                 | 4 | 4    | 4    | 4    | 4  | 4  |
| 8                       | 0.5                | 5           | 4                                 | 2 | 2    | 3(v) | 4    | 3  | 4  |
| 9                       | 0.5                | 10          | 1                                 | 0 | 0(v) | 0(v) | 1(v) | 3  | 4  |
| B. Physiological Saline |                    |             |                                   |   |      |      |      |    |    |
| 1                       | 0.12               | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 2                       | 0.25               | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 3                       | 0.50               | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 4                       | 1.0                | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 5                       | 1.5                | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 6                       | 0.5                | 0.5         | 4                                 |   |      | 4    |      | 4  |    |
| 7                       | 0.5                | 1           | 4                                 |   |      | 4    |      | 4  |    |
| 8                       | 0.5                | 5           | 4                                 |   |      | 4    |      | 4  |    |
| 9                       | 0.5                | 10          | 4                                 |   |      | 4    |      | 4  |    |

Sweating graded on 0 to 4+ scale, 0 being complete anidrosis.

Day 0 refers to testing done immediately after iontophoresis.

(v) = vesicles present in treated area.

Factors: Electrode—anode.

Area—back

Subject No. 21.

These experiments were performed on three other subjects with similar results.

TABLE 5

Time curve of effect of various solutions under anode during iontophoresis in five subjects

| SOLUTION                     | PRESENCE OF SWEATING |   |   |    |                  |   |    |    |                  |   |   |    |                  |   |   |                  |   |   |    |
|------------------------------|----------------------|---|---|----|------------------|---|----|----|------------------|---|---|----|------------------|---|---|------------------|---|---|----|
|                              | Days post treat.     |   |   |    | Days post treat. |   |    |    | Days post treat. |   |   |    | Days post treat. |   |   | Days post treat. |   |   |    |
|                              | 0                    | 4 | 7 | 14 | 0                | 4 | 11 | 21 | 0                | 4 | 7 | 14 | 0                | 4 | 8 | 0                | 4 | 7 | 14 |
|                              | Subject no. 1        |   |   |    | Subject no. 2    |   |    |    | Subject no. 3    |   |   |    | Subject no. 4    |   |   | Subject no. 5    |   |   |    |
| 1. Water, dist.....          | 4                    | 1 | 2 | 3  | 4                | 3 | 1  | 4  | 4                | 3 | 4 | 4  | 4                | 1 | 1 | 4                | 4 | 4 | 4  |
| 2. Sodium chloride.....      | 4                    | 4 | 4 | 4  | 4                | 4 | 4  | 4  | 4                | 3 | 3 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 3. Methylene Blue.....       | 4                    | 2 | 2 | 4  | 4                | 4 | 4  | 4  | 4                | 2 | 4 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 4. Salmine sulfate.....      | 4                    | 4 | 4 | 4  | 4                | 4 | 4  | 4  | 4                | 3 | 3 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 5. Globin hydrochloride..... | 4                    | 4 | 4 | 4  | 2                | 4 | 4  | 4  | 4                | 4 | 4 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 6. Aluminum chloride.....    | 4                    | 4 | 4 | 4  | 3                | 4 | 3  | 4  | 4                | 4 | 4 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 7. Formaldehyde.....         | 4                    | 4 | 4 | 3  | 3                | 2 | 4  | 4  | 4                | 1 | 3 | 4  | 4                | 3 | 4 | 4                | 4 | 4 | 4  |
| 8. Ammonium hydroxide.....   | 4                    | 4 | 4 | 4  | 3                | 4 | 4  | 4  | 4                | 4 | 4 | 4  | 4                | 4 | 4 | 4                | 4 | 4 | 4  |
| 9. Undecylenic acid.....     | 4                    | 2 | 2 | 2  | 4                | 3 | 1  | 4  | 4                | 1 | 3 | 4  | 4                | 3 | 3 | 4                | 4 | 4 | 4  |
| 10. Alcohol, ethyl.....      | 4                    | 1 | 2 | 2  | 4                | 2 | 1  | 4  | 4                | 2 | 3 | 4  | 4                | 2 | 3 | 4                | 4 | 4 | 4  |

Sweating graded on 0 to 4+ scale; 0 representing complete anidrosis.

Factors: Current density 0.5 ma/cm<sup>2</sup>.

Duration of treatment 5 min.

Electrode—anode.

Area—back.



of vesicles by producing a preliminary localized sunburn with ultra-violet light over the area treated later with iontophoresis. Variations in four areas in four subjects were studied and were found to be minimal. The areas studied were arm, back, thigh, anterior chest. No studies were made on the palms or axillae. The majority of our observations have been made on the back.

6. *Repeated treatment:* Repeated treatments spaced several days aparte definitely increased the anidrotic effect.

7. *Season:* With one exception, the experiments were performed in the winter. Two subjects were tested in the summer also. It was found that the threshold current density and time for vesicle formation were significantly reduced in the summer.

### *C. Characteristics and nature of the vesicles*

The vesicles enlarged during sweating, at times coalescing to form bullae. If pricked, clear fluid exuded and sweating became apparent at that site. The walls were so fragile that they could be rubbed off very easily with a towel. The vesicles disappeared spontaneously several hours after sweating ceased.

The vesicles appeared in response to sweating whether due to (1) heat stimulus, (2) exercise, (3) pilocarpine locally or (4) acetylcholine locally. When atropine was injected intradermally to produce local inhibition of sweating, *these vesicles could not be made to appear*. Control studies with saline solution were without effect.

A special technic was employed to further demonstrate the relationship of these vesicles with the sweat gland. Treatment of the skin with 1% methylene blue in aqueous solution under the anode results in selective pin point staining of the sweat pores (19, 20). This makes it possible to identify grossly the sites of the sweat gland orifices in normal skin. After this was done, sweating was normal for several days during a latent period. It was noted at this time that the sweat droplets appeared in the center of the methylene blue dots and in many cases stained rings, described as doughnuts by Abramson (20) were seen as the source of the sweat droplet. Later, when the vesicles appeared they presented, almost without exception, an identifying blue punctum on the very dome. This punctum represented the original sweat gland orifice and served to identify the point of origin of the vesicle. Removal of only this tiny blue speck resulted in the appearance of vesicular fluid. The desquamation of these blue stained points was associated furthermore, with the reappearance of normal sweating.

Tests on anidrotic areas not exhibiting vesicles, revealed that measures which might soften or otherwise remove orificial plugs did not lead to sweating. Such measures included local inunction with anhydrous lanolin, abrasion with emery paper (3/0) or treatment of the area with the cathode during iontophoresis. Moreover the areas were resistant to salicylic acid desquamation. This is in marked contrast to the ease with which sweating can be restored in the event that vesicles are present. Here the simple mechanical trauma of rubbing with a towel removes the tops of the vesicles and sweating is thereby restored to normal.

*D. Histopathology*

Microscopic study of the material obtained from biopsies on 8 subjects can be divided into 2 parts. All biopsies were taken after the subject had been in the heat and sweating for 30 minutes.

1. Control studies on 2 subjects consisted of biopsy of an area of skin one hour after iontophoresis of distilled water ( $\frac{1}{2}$  ma/cm<sup>2</sup>, 10 min.). Prior to the biopsy, testing revealed that sweating in these areas was normal. In these sections the skin appeared quite normal.

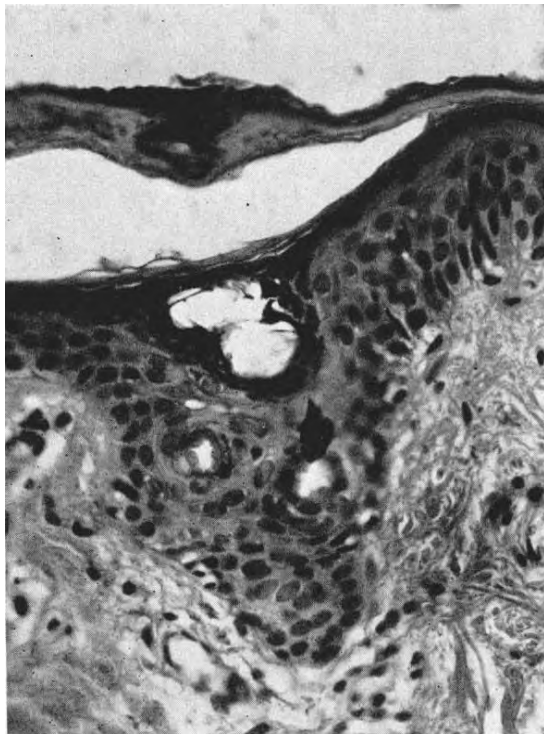


PHOTOGRAPH No. 3. Sweat retention vesicle 80  $\times$ . Iontophoresis (1 ma/cm<sup>2</sup> for 5 minutes with distilled water at the anode) applied 7 days before. Biopsy was taken after 30 minutes of sweating. Serial sections reveal opening at base of vesicle to be continuous with sweat duct.

2. In areas of skin in which post-iontophoretic anidrosis had developed, histopathological examination (6 biopsies) revealed small plaques and plugs of hyper- and para-keratotic stratum corneum at the sweat duct orifices in all cases. In many instances the sweat duct was dilated in its terminal intraepidermal portion (Photograph No. 5). The acini of the sweat gland revealed no definite changes, although some may have been dilated, but this was not susceptible to unqualified evaluation. Other than this no abnormal changes were seen. Vesicles were present to gross inspection in five of these six biopsies. Their characteristics are recorded in the next paragraph.

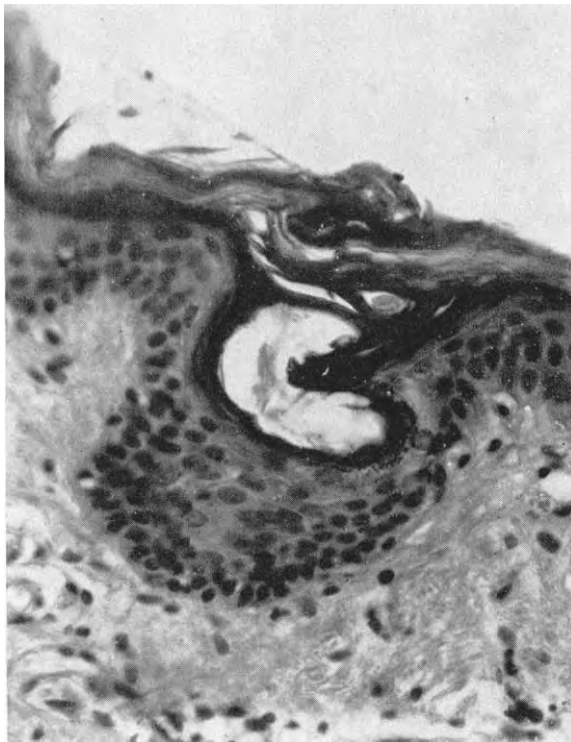


PHOTOGRAPH NO. 4. Sweat retention vesicle 80 X. Iontophoresis (1 ma/cm<sup>2</sup> for 5 minutes with distilled water at the anode) applied 7 days before. Biopsy was taken after 30 minutes of sweating. Note lack of inflammatory infiltrate around sweat duct.



PHOTOGRAPH NO. 5. Sweat retention vesicle 350 X. Iontophoresis (1 ma/cm<sup>2</sup> for 5 minutes with distilled water at the anode) applied 7 days before. Biopsy was taken after 30 minutes of sweating. Close-up of the vesicle shown in No. 4. Note localization of vesicle in hyperkeratotic stratum corneum.

The vesicles lay within hyper- and para-keratotic plaques of stratum corneum (Photographs Nos. 3 and 4). They were filled with clear fluid and with some degenerating stratum corneum cells. Some were elevated, others sunken into the epidermis. On serial section, direct communication with a sweat duct could be demonstrated for each vesicle. Again, the sweat ducts were definitely dilated. No abnormal changes could be seen in the pilo-sebaceous apparatus. Non-inflammatory infiltrate appeared in the cutis. The sweat gland acini were normal in appearance and distribution.



PHOTOGRAPH No. 6. Sweat duct plugging in anhidrotic area without vesicles 350 X. Iontophoresis (1 ma/cm<sup>2</sup> for 5 minutes with distilled water at the anode) applied 7 days before. Biopsy was taken after 30 minutes of sweating. Note dilatation of terminal portion of sweat duct due to blockage by hyperkeratotic plug.

The histopathology supported the thesis that the absence of visible sweating on the skin surface, and the appearance of vesicles during sweating were unequivocal sweat retention phenomena.

#### DISCUSSION

These studies have been directed toward elucidation of the primary effect of iontophoretic current, per se, on the entire sweat gland unit. Over and above current effects is the effect obtained from the introduction into the skin of specific compounds, which act on the sweat gland epithelium. The best example of

this is formaldehyde, which produces anidrosis due to damage to the secretory epithelium (24). This is to be sharply distinguished from anidrosis due to sweat retention within the sweat duct, such as this paper deals with particularly. In any event, these studies reveal no effect of iontophoresis on the secretion of the gland. The findings of significance concerned the duct orifices and the consequent sweat retention anidrosis.

This investigation has shown that it is possible to induce a miliarial type of sweat retention anidrosis and vesicles by means of a single iontophoretic treatment of the skin.

Consideration of various possible explanations for the etiology of this experimental obstruction of the sweat duct has led to the following hypothesis: The iontophoretic current under the positive electrode causes a non-specific injury to the epidermis with a resultant abnormal keratinization. After several days this produces a hyperkeratotic plug of the sweat duct orifices, which serves as a barrier to the flow of sweat onto the surface of the skin. The sweat gland acini are normal and continue to respond to stimuli. In the event of a more marked iontophoretic injury, cohesion between the cells of the stratum corneum is reduced so that under the pressure of entrapped sweat a vesicle forms on the stratum corneum. If higher milliamperages or longer treatment periods are employed, the latent period in which sweating is normal may not be in evidence, due perhaps to initial closure of some of the ducts by periductal edema or to a hardening effect on the epidermis.

A review of the action of iontophoresis per se reveals that it produces injury as a result of complex ionic and electrokinetic phenomena. It does not produce injury by heating the skin, but rather by electrolytic changes (21). For tissues in general, marked differences exist between the reactions at the two poles since at the anode hydrochloric acid and oxygen are liberated with a hardening effect (22). On the other hand, the cathode has a softening effect since it is under this electrode that sodium hydroxide and hydrogen are formed. The dose varies with the size of the electrode, the smaller electrode permitting the use of higher current densities (21). The current densities employed in this study were well within the safe range (23).

The difference in epidermal changes under the two electrodes reflects the specificity of the anode or hardening electrode as the occasion for the induction of sweat duct obstruction. All of the findings in regard to current density and time were in keeping with the degree of reaction to be expected. The use of various solutions or water alone under the electrode without striking differences indicates that the effect is to be directly related to iontophoresis rather than to the effect of introducing a particular compound into the skin.

#### NATURE OF CONTENTS OF VESICLES

It is concluded that the vesicles contained sweat (rather than serum for example) for the following reasons:

(1) they appeared and enlarged during exposure to high temperatures or chemical stimuli for sweating, disappearing regularly in the cool;

(2) they could not be made to appear in areas where the sweat gland was inactivated by the parasympatholytic drug, atropine; and

(3) they appeared at the site of sweat pores and on biopsy were located in direct communication with the sweat duct.

#### EXPLANATION OF ANIDROSIS

The explanation of the dry anidrotic state of areas following iontophoresis was more difficult. One possibility to be considered was that the current damaged the function of the acini of the sweat glands. This is unlikely since the glandular tissue is deeply imbedded in the cutis below the superficial level which iontophoresis affects. Moreover, the use of stronger iontophoretic currents or longer treatment periods leads to the production of sweat vesicles, which are dependent upon normal glandular secretory activity. This would serve to dispel the idea that iontophoresis damages the acinar tissue. Damage to the sweat duct of an obstructive or destructive nature is the alternate possibility. Biopsy sections reveal obstructive damage as the proper explanation. Keratin plugs and caps can be seen at the sweat duct osita. The ducts are dilated directly below, which indicates functional patency of the duct to the uppermost level as well as evidence of secretion of sweat.

#### THE QUINIZARIN TECHNIC

This technic for grading sweating has limitations. A zero reading does not mean that absolutely every single gland is inactivated since insignificant quantities of sweat could still be secreted and pass through the dye without discoloration. Furthermore, evaluation can not be made in a hot *dry* atmosphere since the sweat evaporates too rapidly to be graded. Attention should be directed to the fact that sweating can be depressed somewhat and still rate as 4 plus in the system of grading since quantitative differences exist beyond the point of producing a purple color change over the whole area. Nonetheless, the method was admirably suited to this study because the conditions were uniform and otherwise favorable.

#### INSENSIBLE PERSPIRATION

Since direct gravimetric analysis is necessary for determination of insensible perspiration, nothing can be said of the effect of iontophoresis on insensible perspiration, through the areas treated. However Pinson (25) has shown that iontophoresis of formaldehyde is without effect on insensible perspiration.

#### COMPARISON OF MILIARIA CRYSTALLINA, MILIARIA RUBRA, TROPICAL ANIDROSIS AND SWEAT RETENTION ANIDROSIS

It is not within the scope of this presentation to discuss this subject. It will be dealt with in a subsequent communication. However, in our judgment, the experimental vesicular eruption was identical, clinically and histopathologically, with that seen in miliaria crystallina (2).

## SUMMARY

Local sweat retention anidrosis and sweat retention vesicles were produced experimentally in man by a single treatment of the skin with iontophoresis.

On the basis of physiologic and histologic study, it appeared that a minor superficial epidermal injury was produced, not affecting the acini of the sweat gland, with a resultant hyperkeratosis which led to a transitory sweat duct obstruction. This resulted in local sweat retention anidrosis and vesicles containing sweat on stimulation of the sweat gland.

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## REFERENCES

1. ROBINSON: Miliaria and sudamina. *J. Cutan. & Vener. Diseases*, **2**: 362, 1884.
2. ROBINSON, A. R.: Hidrocystoma. *J. Cutan. & Genito-Urinary Diseases*, **11**: 293, 1893.
3. SULZBERGER, M. B. AND ZIMMERMAN, H. M.: Studies on prickly heat. *J. Invest. Dermat.* **7**: 61, 1946.
4. O'BRIEN, J. P.: A Study of miliaria rubra, tropical anhidrosis and anhidrotic asthenia. *Brit. J. Dermat.*, **59**: 125, 1947.
5. ALLEN, S. D. AND O'BRIEN, J. P.: Tropical anidrotic asthenia—a preliminary report. *Med. J. Australia*, **31**: 325, 1944.
6. SULZBERGER, M. B., ZIMMERMAN, H. M. AND EMERSON, K.: Tropical anidrotic asthenia (thermogenic anhidrosis) and its relationship to prickly heat. *J. Invest. Dermat.*, **7**: 153, 1946.
7. PICK, W.: Pathogenesis of Fox-Fordyce disease. *Arch. Dermat. & Syph.*, **13**: 782, 1926.
8. YAMAGUCHI, T. AND KATO, G.: Ein Beitrag zur Pathogenese des Hidrocystoms. *Jap. J. Derm. & Urol.*, **46**: 29, 1939.
9. DOSTROVSKY, A. AND SAGHIER, F.: Experimentally induced disappearance and reappearance of lesions of hidrocystoma. *J. Invest. Dermat.*, **5**: 167, 1942.
10. SULZBERGER, M. B., HERMANN, F. AND ZAK, F. G.: Studies of sweating I. Preliminary report with particular emphasis on a sweat retention syndrome. *J. Invest. Dermat.*, **9**: 221, 1947.
11. SCHWARTZ, L. AND PECK, S. M.: *Cosmetics and Dermatitis*, p. 163. 1946. Paul B. Hoeber, New York.
12. POLLITZER, S.: Prickly heat, lichen tropicus, miliaria papulosa, M. rubra, etc. *J. Cutan. & Genito-Urinary Diseases*, **11**: 50, 1893.
13. LOBITZ, W.: In discussion. *J. Invest. Dermat.*, **9**: 240, 1947.
14. MILENKOW, S. M.: Ein Fall von Verstopfung der Schweissdrusen bei Pellagra. *Virchow Arch. f. Path. Anat.*, **297**: 410, 1936.
15. DAVIDSON, C. S., WILCKE, H. L. AND REINER, P. J.: A nutritional survey of starvation in a group of young men. *J. Lab. & Clin. Med.*, **31**: 721, 1946.
16. SCHIDACHI, T.: Experimentelle erzeugungen hidrocystomen. *Arch. f. Dermat. u. Syph.*, **83**: 3, 1907.
17. ABRAMSON, H. A. AND ALLEY, A.: Skin Reactions. I. Mechanism of Histamine Iontophoresis from Aqueous Media. *Arch. Physical Therapy*, **18**: 327, 1937.
18. GUTTMANN, L.: A Demonstration of the study of sweat secretion by the Quinizarin method. *Proc. Roy. Soc. Med.* **35**: 77, 1941.
19. ICHIHASHI, T.: II. The paths of cataphoresis in the skin and the influence of perspiratory conditions on the cataphoretic effect. *J. Oriental Med.*, **25**: 103, 1936.

20. ABRAMSON, H. A. AND ENGEL, M. G.: Skin reactions. XII. Patterns produced in the skin by electrophoresis of dyes. *Arch. Dermat. & Syph.*, **44**: 190, 1941.
21. MOLITOR, H. AND FERNANDEZ, L.: Studies on iontophoresis. I. Experimental studies on the causes and prevention of iontophoretic burns. *Am. J. M. Sc.*, **198**: 778, 1939.
22. KOVACS, R.: Principles and Practice of Physical Therapy. Vol. III, Chapt. 9. 1939. F. A. Davis Co. Philadelphia.
23. SHAFFER, L. W.: Ionic medication in dermatology. *Arch. Dermat. & Syph.*, **23**: 287, 1931.
24. ICHIHASHI, T.: III. The antisudorific effect of formalin by cataphoretic application and its practical use. *J. Orient. Med.* **25**: 105. 1936.
25. PINSON, E. A.: Evaporation from human skin with sweat glands inactivated. *Am. J. Physiol.* **137**: 492. 1942.

### DISCUSSION

*Dr. Theodore Cornbleet*: I had the opportunity of observing a colored man whose injury to the back resulted in paraplegia. Above the line of paralysis, there were episodes of sweating; below this, the skin remained dry. After some time, the patient developed miliaria on the part of the trunk not paralyzed. A histological study showed the presence of keratotic plugging at the sweat ductal orifices, as others have previously found. The factor of heat in inducing sweating was absent in our case.

A number of inquiries were undertaken to explore the background of miliaria. Nothing remarkable was found, not even in the studies of vitamin A metabolism. The results of one type of examination may be worthwhile mentioning here. The Burchardt modification of the Lieberman reaction for cholesterol was used on biopsy sections. This is a histochemical procedure. There was a distinct diminution in the amount of cholesterol in the epidermis of our patient as compared to that found in normal controls. Reduced quantities of cholesterol were present, too, in the epidermis removed from the dry skin free of miliaria overlying the paralyzed sites.

Thus, the decreased cholesterol in the epidermis could not of itself have been the immediate cause of miliaria in our patient. It may be conjectured, however, that the profuse sweating acting on a terrain impoverished of cholesterol induced hyperkeratinization of the sweat pores. The mechanical obstruction of the sweat duct ostia by these plugs brings in its train the changes seen in miliaria.

*Dr. Marion B. Sulzberger*: I had a very rough trip getting here, but would gladly have flown twice as long in weather twice as rough in order to have the opportunity to hear this paper. To me it is an interesting, stimulating and promising study, and I want to compliment the authors. I should like to say only that it looks to me as though our old friend, the concept of "dysidrosis", were back again—and back to stay. When one can see vesicles of this kind produced experimentally, and sees that they are due to a disturbance of sweating—i.e. to blocking of the sweat pores—it does not take much imagination to get the idea that clinical types of vesicular eruptions—and even some non-vesicular ones—may be based on just such sweat retention. Included prominently among these clinical vesicular eruptions is that bugaboo—that great unknown—often called "recurrent vesicular eruptions of the hands and feet." These, as is well



known, are not infrequently associated with disturbances of sweating, particularly hyperhidrosis. Moreover, I think that not only prickly heat and "dysidrosis", or papulo-vesicular and pustular eruptions of the hands and feet, but many other skin diseases and symptoms, such as itching, must be considered in relationship to this phenomenon of sweat gland plugging. In addition, this plugging may account for many systemic disturbances associated with the inability to cool, based on the inability to pour out fluid on the skin's surface when it is necessary to do so for cooling purposes. All these cutaneous and systemic lesions and symptoms may be among those which Franz Hermann, F. Zak and I have included in what we call the "Sweat-Retention Syndrome" (*J. Invest. Dermat.* **9**: 221 (Nov.) 1947).

*Dr. Peter N. Horvath:* I would like to mention that what we think we have produced here is miliaria crystallina, as opposed to miliaria rubra. These vesicles are in the stratum corneum. We have never had them associated with any inflammation. We have considered the question of fat content of the skin in relation to these vesicles as such a study was carried out by O'Brien, who could produce miliaria by defatting the skin. Our feeling has been that on the normal subjects in our series, the production of these vesicles depended on the response of the skin to non-specific injury, and all the substances we have used have contributed to this opinion. Also, there has been a great individual variation, namely, fair-skinned types would need minimal injuries to produce these vesicles, whereas on the darker skinned individuals a great deal of stimulation was necessary to produce them.