

# Disorders of Transepidermal Elimination

## Part 2

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**T**ransepidermal elimination is a disorder in which dermal stimuli profoundly effect the behavior and structure of the overlying epidermis. Briefly, there are two categories of disorders: the first are primary dermatoses and consist of elastosis perforans serpiginosa and reactive perforating collagenosis; the second group originates from alterations of dermal constituents in preexisting disorders which induces transepidermal elimination. Some examples are perforating granuloma annulare, pseudoxanthoma elasticum, sarcoid, lichen nitidus, and several others. The following is a review of the latter group.

### Perforating Granuloma Annulare

Granuloma annulare (GA) is a benign granulomatous skin disorder consisting of flesh-colored papules arranged in an annular or arciform pattern. Histologic features include focal areas of altered "necrobiotic" collagen surrounded by palisading mononuclear phagocytes. Several subtypes of this disorder exist including subcutaneous varieties. Recent articles have emphasized the other variants, such as generalized perforating GA<sup>1,2</sup> and perforating GA.<sup>3,4</sup>

#### History

Perforating GA (PGA) was initially described by Pinkus in 1934<sup>5</sup> and then nearly two decades later by Civatte<sup>6</sup> in 1952 in five patients who were given the erroneous diagnosis of tuberoulcerative or gummatous GA. Calnan<sup>7</sup> presented another patient in 1954. The present concept of TE in PGA was not fully elucidated until 1971, when Owen<sup>8</sup> described two patients with small nodular lesions with central

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umbilication on the margins of the fingers and on the hands.

#### Clinical Characteristics

We have reviewed 22 cases of PGA described in the literature (Table 1). The average age of onset was 29 years, with a female:male ratio of 16:6. Most lesions were described as flesh- or red-colored, asymptomatic, 3–4-mm papules with central umbilication. Most (95%) occurred on the extensors of the extremities, especially on the dorsa of the hands. Other sites included the face, back and shoulders. The Koebner phenomenon was not noted. While most reports specifically reported sparing of the palms and soles, one presents the unique appearance of round, grouped papules with a 2–8-mm central umbilication present on the palms.<sup>9</sup> Another describes lesions on the soles.<sup>10</sup> Usually the papules of PGA do not drain, but two patients' lesions have been shown to exude a thick, creamy<sup>7</sup> or cheesy<sup>11</sup> material. Individual lesions resolve over months, leaving a hyper- or hypopigmented area, but the disease may continue for many months. Although a recent review suggests that diabetes may be associated with GA,<sup>12</sup> only three of the reported cases of PGA, were in patients with diabetes.<sup>6,9,11</sup>

#### Histology

At a single time, only a few papules are in the active state of perforation; therefore, serial sections on several lesions must be performed or the diagnosis may be missed.<sup>13–15</sup> Examination of the epidermal

This is the second in a series of two articles.  
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FIG. 1. Lesions of perforating granuloma annulare (PGA) are seen as umbilicated papules on the dorsa of the hand. Note that there is not a strict linear pattern to the configuration.

perforating canal with special stains shows a plug consisting of cellular debris, altered collagen, and mucinous material. The epidermal perforation communicates with small areas of GA in the dermis that consist of altered ("necrobiotic") collagen surrounded by palisading mononuclear phagocytes in the dermis. The necrobiotic area is superficial in the papillary dermis and can be seen to form the floor of the canal as the altered collagen is actively extruded.

#### *Generalized Perforating Granuloma Annulare*

Generalized PGA was first described by Duncan et al.<sup>13</sup> in two children with multiple flesh-colored papules on the extensors of the extremities, many of them with a central dell, some with a tiny central scab. The papules were 1–4 mm in diameter and regressed spontaneously. Since this initial report, there have been at least seven patients described (Table 2).<sup>1,2,13–16</sup> There are probably five additional cases of generalized PGA from the given clinical description, but TE could not be substantiated because histologic serial sections were not performed.<sup>13</sup> The average age of onset was 17 years. Most patients have hundreds of lesions, often numbering greater than 300 flesh- to rust-colored papules,<sup>1,10,14</sup> usually 3–4 mm in diameter, with umbilicated crusted centers.

Initially, some skin-colored to red papules appear and are associated with erythematous halos.<sup>13</sup> These increase in size and develop a yellowish center with a central umbilication. The course is similar to that of localized PGA. The extensors of the extremity are the most common site. Rarely, the cheeks, face, interscapular region, and pinna of the ear may be

involved. The palms and soles usually are not affected. Three of the patients specifically noticed exacerbation of the eruption during the summer, and one of these reported total clearing during the winter.<sup>13,14</sup> Two of the patients reported pruritus<sup>2,13</sup> and only one patient reported the presence of diabetes.<sup>16</sup>

#### *Transfollicular Elimination of Granuloma Annulare*

Bardach<sup>17,18</sup> described two patients, a 42-year-old woman in good health and a 68-year-old diabetic man, both with asymptomatic red papules, on the hands in the former and on the neck, upper chest, and shoulders in the latter. Histologic examination revealed elimination of necrobiotic material via the follicular epithelium from an adjacent palisading granuloma.

#### *Association with Other Disorders*

There is no evidence to associate PGA with internal disease, although of the 29 patients with generalized and isolated PGA described in the literature, four had diabetes mellitus,<sup>6,9,11,16</sup> two had pulmonary tuberculosis,<sup>6,19</sup> one had progressive neural atrophy,<sup>10</sup> one had Down's syndrome,<sup>20</sup> and another 7–9% eosinophilia.<sup>14</sup> Dick and Syme reported a case of PGA in association with scleritis, with concurrent onset and resolution of both disorders.<sup>4</sup> An interesting observation by Aliaga et al.<sup>3</sup> and Carton et al.<sup>21</sup> concerns their patients who had been consuming vitamin D prior to the occurrence or reappearance of PGA. Aliaga's patient had been ingesting vitamin D 600,000 IU/week for a total of 2 years. Twelve papules of PGA appeared on the dorsa of his fingers. No Koebner phenomenon was seen. Discontinuation of the vitamin resulted in complete clearing within 40 days.<sup>3</sup>

PGA is a disease of unknown etiology, although the basic pathogenesis of GA has been postulated to involve immune complexes<sup>4</sup> with participation of the helper-inducer T cell subset.<sup>22</sup> Several pathogenic or precipitating factors have been implicated, including insect bites,<sup>8</sup> ultraviolet radiation,<sup>13,14</sup> vitamin D administration,<sup>3,21</sup> and trauma.<sup>15</sup> Smith and Goette<sup>15</sup> attempted to induce lesions experimentally in their patients with liquid nitrogen, cantharidin, needle pricks, and ultraviolet light A and B, with no success. This experimental evidence and the fact that the majority of reports specifically deny the presence of the isomorphic response strongly suggest that sunlight and trauma have very little to do with the pathogenesis of this disorder.

TABLE 1. *Perforating Granuloma Annulare*

Author	Age	Sex	Onset	Clinical Description	Course/Comments
Smith <sup>15</sup>	37	M	29	3-4-mm papules on extensors of extremities, dorsa of wrists and fingers (10 of 60 lesions umbilicated)	Topical steroids helped
Aliaga <sup>3</sup>	10	M	8	3-4-mm papules on dorsa of fingers, 12 in number, central umbilication	Stopped intake of vitamin D with complete resolution
Gattlen <sup>23</sup>	30	F	30	10-15 papules (3-4 mm) with central umbilication on fingers	Resolved in 6 months
	46	F	46	3-5-mm papules with central umbilication on face and hands	
	27	F	26	26 umbilicated papules on hands	
	28	F	28	3-5-mm papules	
	17	F	1	3-5-mm papules on hands	
Van der Meer <sup>9</sup>	22	F	"Very early age"	2-8-mm papules with central umbilication on extensors of extremities and palms	
Owens <sup>8</sup>	22	F?	17	Skin-colored with umbilication on dorsum of hands	Good response to topical steroids
	11	F	—	Typical appearance on hands and fingers	
Agren-Jonsson <sup>19</sup>	58	F	—	Extensors, back, shoulders involved	Treated with chloroquine, sulphur, dapsone, and anti-tuberculous drugs without effect
	18	F	—	Red papulo-nodules	
	52	F	32	Symmetric on trunk and limbs with atrophic scars	
Tan <sup>11</sup>	72	M	72	Bluish-red plaque on flexor of wrist with many plugged and crusted sinuses, discharging cheesy material	
Dick <sup>4</sup>	60	M	60	5-mm red nodules with ulceration then small scars. Some heal with scars.	Resolution in 2 years without treatment. Associated and resolved simultaneously with scleritis.
Calnan <sup>7</sup>	26	M	25	Symmetric eruption of small nodules on backs of hands and fingers, pale lilac tint with central plug, without scars. Discharges creamy, thick fluid.	
Civatte <sup>6</sup>	—	F		Face	
	42	F			
	—	F			
	—	M			
	43	F	7		
Mehregan <sup>71</sup>				Several cases of perforating GA	
Carton <sup>21</sup>	19	F			

### Diagnosis

The disease that most nearly mimicks the appearance and location of PGA is reactive perforating collagenosis. Clinically, PGA (in contrast to RPC) is not associated with the Koebner phenomenon. PGA tends to occur a decade later and is not closely associated with diabetes. Resolution of individual

lesions is slow, sometimes taking years, compared with 1-2 months in RPC. The histology of PGA is also characteristic with TE of a central necrobiotic mass with peripheral phagocytes. Furthermore, there are no vertically oriented collagen fibers (which can be seen in RPC). At the base and adjacent areas of PGA lesions are the typical histologic picture of GA. Histology excludes other disorders with a similar

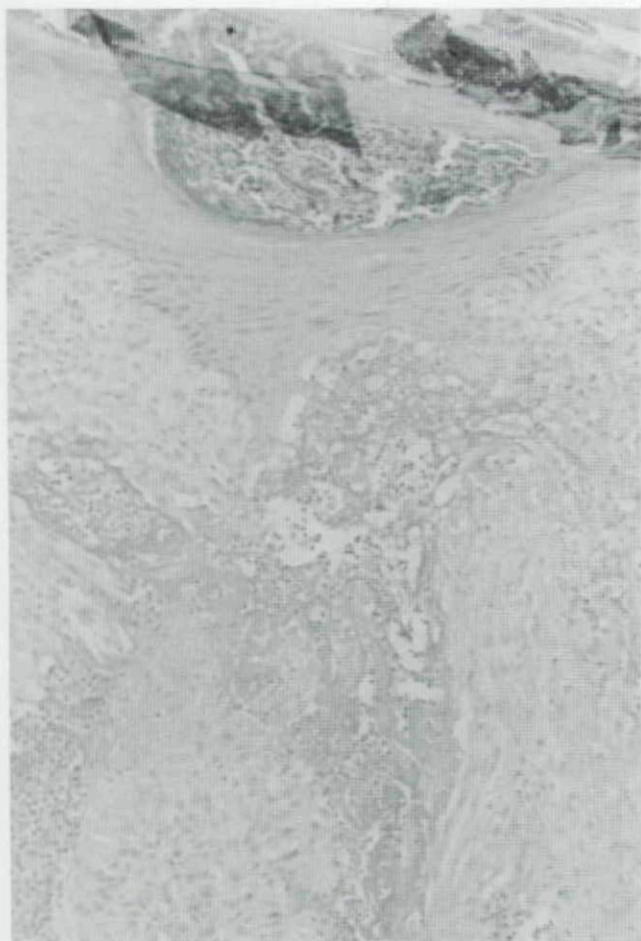


FIG. 2. The typical histology of granuloma annulare can be seen at the base of a lesion of perforating granuloma annulare. This patient also had concurrent Henoch-Schonlein purpura. ( $\times 100$ ) (Courtesy of Donald Clemons, M.D.)

clinical appearance, such as Kyrle's disease, EPS, keratocanthoma, pityriasis lichenoides et varioliformis acuta, and molluscum contagiosum.

#### Treatment

Treatment of this disorder has consisted of topical steroids with occlusion, which have helped considerably in some patients<sup>8,15,23</sup> but not in others.<sup>1</sup> Oral prednisone induced remission within 1 month with no recurrences in one patient (total dose, 500 mg).<sup>10</sup> Topical treatments found to be unsuccessful include topical steroids without occlusion,<sup>20</sup> salicylic acid,<sup>9</sup> and liquid nitrogen.<sup>9,15</sup> Other unsuccessful agents included chloroquine, sulfur, dapsone, and antituberculous agents,<sup>19</sup> ultraviolet light<sup>15,19</sup> vitamin B<sub>6</sub>, and iodobismitol.<sup>19</sup> Spontaneous remission may also occur.<sup>13</sup>

### Transepidermal Elimination of Sarcoidal Granulomas

Another example of TE of granulomas was reported by Batres.<sup>24</sup> A 24-year-old black man with a diagnosis of sarcoidosis had TE discovered during a routine chest x-ray. It was confirmed on biopsy of mediastinal nodes. On examination, he had similar-appearing lesions present on the scalp, cheek, and mandible. Lesion sizes ranged from 5.6 cm on the scalp to 0.8 cm on the mandible. Biopsy examination of the scalp showed several sarcoid granulomas composed of epithelioid cells scattered throughout the dermis. The more superficial granulomas were in contact with the epidermis, with resulting pseudoepitheliomatous hyperplasia. Portions of the granuloma were seen to be engulfed by the epidermis, while another portion appeared within a cup-shaped depression at the surface of the epidermis. These findings were consistent with TE of sarcoidal granulomas.

### Perforating Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is a genetically inherited generalized disorder of connective tissue considered to be divided into two autosomal dominant (AD) and two recessive (AR) variants. This systemic disease is characterized by childhood onset and involves the eyes with angioid streaks, gastrointestinal tract, cardiovascular system, and the skin. Cutaneous findings include groups of small, yellow papules in the flexural folds, especially involving the neck, axillae, groin, antecubital fossa, and umbilicus.

#### History

The earliest case of perforating PXE occurred in 1962, when Schutt<sup>25</sup> reported a 33-year-old man with PXE and a 1-year history of a persistent papular eruption. The patient had closely grouped, brown, discrete, hyperkeratotic papules aggregated in the left axillae and 3 cm above the umbilicus. Although Schutt considered this a case of "reactive perforating elastosis" (EPS) occurring in a patient with PXE, it was later shown by Lund and Gilbert<sup>24</sup> to be the first definite case of perforating PXE.

#### Clinical Characteristics

To date, there have been at least 18 cases of perforating PXE reported in the literature. Table 3 lists the cases and describes the salient features of each.<sup>27-35</sup> The youngest individuals were 16- and 17-

TABLE 2. Generalized Perforating Granuloma Annulare

Author	Age of Presentation (Yrs.)	Sex	Onset Yrs.	Site	No.	Size (mm)	Description	Diabetes	Course
Hazelrigg <sup>1</sup>	19	F	19	Knees to dorsa feet	500	1	Rust and flesh colored with umbilicated crusted centers, other flat and shiny. Down's syndrome.	—	No response to topical steroids.
Duncan <sup>13</sup>	3	M	3	Extensors of extremities	50	1-2	Flesh colored papules with central dell or scab with occasional macules and scars. Erythematous halo with moderate pruritus.	No	Resolve completely in winter.
	6	F	3	Extensors of extremities, sparse on back	50	3-4	Similar to above.	No	Exacerbation in summer
Izumi <sup>14</sup>	6	F	2	Sun exposed extensors of extremities, rarely on trunk	300	1-3	Papular lesions, one third umbilicated.	—	Exacerbation in summer
Jacyk <sup>10</sup>	42	F	41	Extensors of extremities, face, interscapular, soles, pinna of ears	500	3-5	Erythematous papules with central umbilication with discharges clear fluid.	No	Prednisone cleared lesions
Bauman <sup>2</sup>	6	F	6	Arms, extremities, cheeks, sparsely elsewhere	Many	5	Flesh colored papules with umbilication, no discharge.	—	—
Delaney <sup>16</sup>	60	M	48	Extensors of lower extremities, calf but sparsely all over, sparing palms, soles and face	Many	Small	Red papules with yellow center with discharge of clear fluid.	Yes	—

TABLE 3. Summary of Cases of Perforating Pseudoxanthoma Elasticum

Race	Sex	Author	Age	Angoid	Diminished Pulses or Calcification	Hypertension	Location Periumbilical?
?	F	Bos <sup>30</sup>	26	Yes	—	—	Yes
?	F	Schwartz <sup>13</sup>	59	Yes	—	Yes	Yes
?	F	Lund <sup>26</sup>	48	Yes	—	Yes	Yes
White	M	Schutt <sup>25</sup>	35	No	Yes	—	Upper abdomen
White	M	Graham <sup>35</sup>	17	No	—	—	Abdomen
White	M	Smith <sup>27</sup>	33	Yes	Yes	—	Yes
Black	F	Hicks <sup>29</sup>	58	No	—	Yes	Yes
Black	F	Hicks <sup>29</sup>	55	No	—	Yes	Yes
Black	F	Hicks <sup>29</sup>	58	No	—	Yes	Yes
Black	F	Hicks <sup>29</sup>	57	No	—	Yes (also diabetes)	Yes
Black	F	Hicks <sup>29</sup>	56	No	—	Yes	Yes
Black	F	Hicks <sup>29</sup>	57	—	—	—	Yes
Dark	F	Premalatha <sup>28</sup>	45	No	—	Diabetes only	Yes
?	F	El Mofty <sup>34</sup>	38	No	—	—	Right arm
?	F	El Mofty <sup>34</sup>	44	No	—	—	—
Black	F	Caro <sup>32</sup>	33	No	Yes	Yes	Yes
White	M	Caro <sup>32</sup>	16	No	Yes	—	Yes
Black	F	Pai <sup>31</sup>	52	—	—	—	Yes

TABLE 4. Comparison of Clinical Properties of Autosomal Dominant and Recessive-type PXE<sup>36</sup>

Characteristics	Dominant 1: # of Patients (%)	Dominant 2: # of Patients (%)	Recessive 1: # of Patients (%)	Recessive 2: # of Patients (%)
Classical, peau d'orange and flexural rash	12 (100)	12 (24)	40 (77)	—
Macular rash	—	35 (70)	7 (13.9)	—
General cutaneous PXE	—	—	—	3 (100)
Vascular disease				
Angina	7 (56)	—	—	—
Claudication	7 (56)	—	—	—
Hypertension	9 (75)	4 (7.8)	10 (19.7)	—
Ophthalmologic abnormalities				
Severe choroiditis	9 (75)	4 (7.8)	18 (35)	—
Angioid streaks	4 (34)	24 (47)	24 (47)	—

year-old men, the rest were older than 30 years of age. The average age of onset was 43 years in 14 women and 4 men. Most patients were black or of Mediterranean origin. Periumbilical location of the lesions occurred in 89% of the patients; less frequent sites were the sides of the neck, upper arm, anterior chest, axillae, groin, and back. The typical clinical appearance of perforating PXE consists of closely clustered, well-demarcated, soft, brown, hyperkeratotic papules in a periumbilical location.<sup>28</sup> Several papules may coalesce into a tender verrucous plaque, up to 14 cm in size, with hyperkeratotic papules at the periphery. Occasionally "purulent" material may exude from the border of the plaque.<sup>26</sup> Infrequently, a well-demarcated, hyperpigmented, reticulated, atrophic patch with discrete, scattered, keratotic papules at the periphery of the lesion may occur.<sup>29</sup> Pruritus is a variable feature. As opposed to other perforating dermatoses, perforating PXE is typically characterized not by discrete umbilicated papules, but by clustered keratotic papules at the periphery of a verrucous plaque. Only three patients had umbilicated papules.<sup>25,27,30</sup>

Vascular disease, such as hypertension, claudication, diminished pulses, or angina, were found in 11 (61%) patients with perforating PXE. Angioid streaks were reported in 4 patients (22%), while 12 patients (67%) were stated specifically not to have angioid streaks. Considering the AD and AR forms (types 1 and 2) of PXE as defined by Pope,<sup>36</sup> vascular disease is not a feature of the AD type 2 nor AR type 1 or 2 (less than 20%). On the other hand, vascular disease occurs in 75% and angioid streaks in 34% of individuals with Pope's AD type 1 (Table 4). In this respect, patients with perforating PXE most closely resemble Pope's AD type 1 in regard to vascular and ocular involvement.

### Histology

Lund and Gilbert<sup>26</sup> have succinctly and clearly differentiated perforating PXE from EPS that occurs in association with PXE. Histologically, PXE is a distinct entity characterized by mild acanthosis with basophilic elastic fibers in the midreticular dermis with an adjacent foreign body reaction. The elastic fibers are curled, granular, fragmented, and calcified. Accordingly, perforating PXE is characterized and differs from EPS by the presence of short, gnarled, calcified, basophilic elastic fibers that are being transepidermally eliminated.<sup>26</sup> Idiopathic EPS, on the other hand, is characterized by straight noncalcified eosinophilic elastic fibers (except in elastomas) and is not associated with any systemic involvement. Lund and Gilbert reviewed the literature and found that only one case reported as EPS in association with PXE clearly established the presence of the two diseases. Furthermore, this single case had unusual features not typical of EPS. In addition, one other case that they did not include did not establish the presence of EPS in a patient with documented PXE.<sup>37</sup> It is probable that almost all cases reported as EPS occurring in patients with PXE are actually perforating PXE. Since the publication of Lund and Gilbert's paper, there have been no reported cases of EPS in association with PXE, as all subsequent reports have been described as perforating PXE.

### Transepidermal Elimination of Lichen Nitidus

An otherwise healthy 8-year-old boy with an asymptomatic rash on the trunk and extremities of several months duration was reported by Bardach.<sup>38</sup> Close inspection disclosed multiple pin-sized, round, flesh-colored, shiny papules distributed over the arms,

trunk, and legs favoring the extensor surfaces. Biopsy from an elbow lesion showed characteristic features of lichen nitidus. However, serial sectioning revealed the presence of a discrete dermal infiltrate lying at the base of a transepidermal perforating channel, in communication with the surface.

### Transepidermal Elimination of Papular Mucinosis

Bard<sup>39</sup> recently described a case of TE of papular mucinosis. This 50-year-old woman with long-standing scleromyxedema, confirmed on previous biopsy, developed asymptomatic 1-2-cm nodules with a central adherent keratotic plug within yellow doughy plaques on the extensor aspects of her upper extremities. These were resistant to treatment.

On histologic evaluation, the epidermis was acanthotic, hyperkeratotic, and hyperplastic with the formation of a transepidermal channel filled with alcian blue-positive material in direct communication with the dermis. The dermis contained fibroblast proliferation with intensely eosinophilic collagen bundles and was positive on alcian blue stain, indicative of acid mucopolysaccharides. These changes were consistent with TE of mucinous material present in lesions of scleromyxedema.

### Perforating Rheumatoid Nodule

Although transepidermal elimination of rheumatoid nodules is probably quite common, it was not until Horn and Goette<sup>40</sup> in 1982, drew attention to this interesting phenomenon. Their 54-year-old woman patient with rheumatoid arthritis developed periarticular nodules with a central core. The striking histologic feature was TE, with a remarkable depth of extrusion. The acanthotic crater traversed the entire thickness of the dermis with a column of necrobiotic material extending from the deep dermis to the epidermis and extruding through the crater. They postulated that this was possibly a case of transdermal elimination in conjunction with transepidermal elimination.

### Transepithelial Elimination in Necrobiosis Lipoidica

Parra<sup>41</sup> described three cases of adult-onset diabetics with lesions typical of necrobiosis lipoidica, mostly on the extremities. Around the periphery of the necrobiosis lipoidica lesions were brown, comedo-like plugs that could be removed on scraping with a curette, leaving a crater-like depression.

Histologic examination of their biopsies was con-

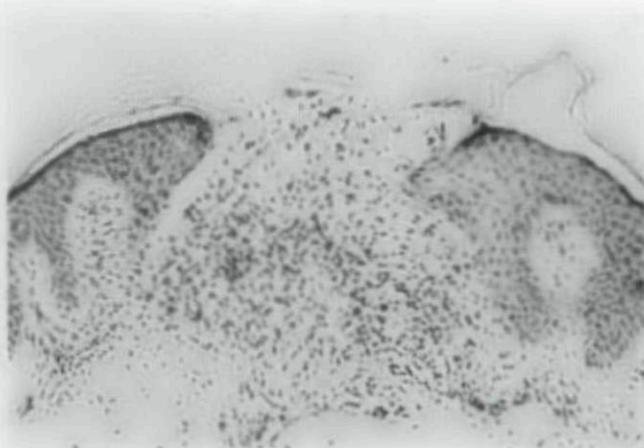


FIG. 3. Histology of an umbilicated papule of lichen nitidus demonstrating TE. (X250) (Courtesy of Harald G. Bardach, M.D.)

sistent with necrobiosis lipoidica, but in all specimens examined there was elimination of a band of altered "necrobiotic" collagen via a transfollicular route. The epidermis was acanthotic and hyperkeratotic. Garcia et al.<sup>42</sup> reported a similar condition.

Parra postulated that the process of transepithelial elimination through the follicular wall may lead to the destruction of the hair follicle. This in turn may explain the absence of epidermal appendages, which is a common finding in long-standing necrobiosis lipoidica.

### Transepithelial Elimination of Infectious Agents

Several examples of TE of bacterial,<sup>43</sup> protozoal,<sup>44</sup> and fungal<sup>45,46</sup> pathogens have been reported in the

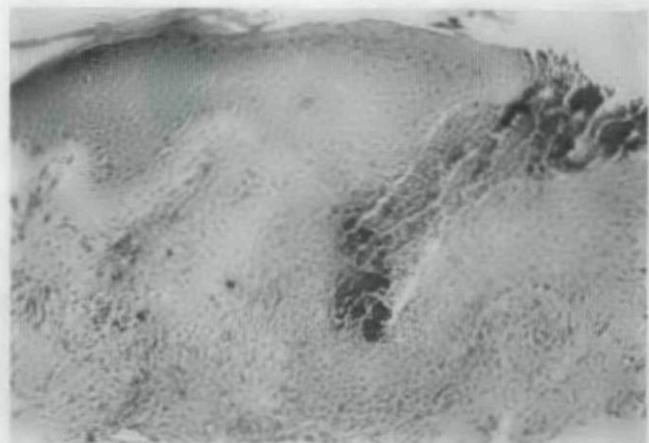


FIG. 4. TE of staphylococcal aureus in botryomycosis. (X100) (Courtesy of Detlef K. Goette, M.D.)

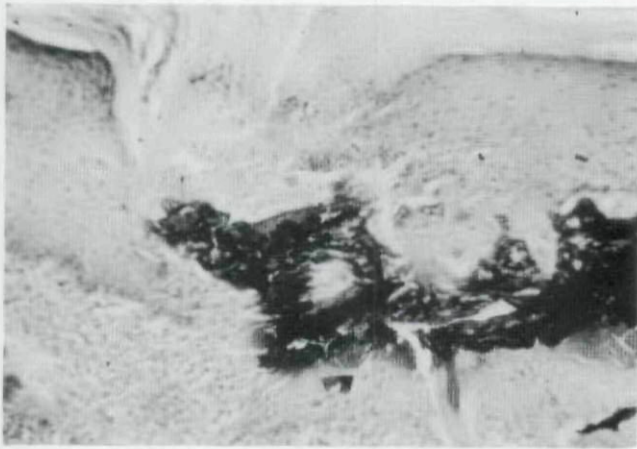


FIG. 5. Calcinosis cutis following electroencephalography using a calcium containing electrode paste. Note TE of the calcium particles. (X100) (Courtesy of Amir H. Mehreghan, M.D.)

literature. Goette,<sup>43</sup> a prominent figure in the field of TE, recently described a case of botryomycosis (actinophytosis due to staphylococcal aureus) in a 76-year-old man with a clinical lesion that appeared as a basal cell carcinoma with a central erosion. Wood et al.<sup>44</sup> reported a 33-year-old man with neurologic symptoms secondary to schistosomiasis who developed flesh- and erythematous-colored papules arranged in an arcuate configuration. A biopsy specimen revealed schistosomal ova within dermal granulomas perforating through the epidermis. Biopsy specimens from both patients revealed TE of the infectious agents with pseudoepitheliomatous hyperplasia of

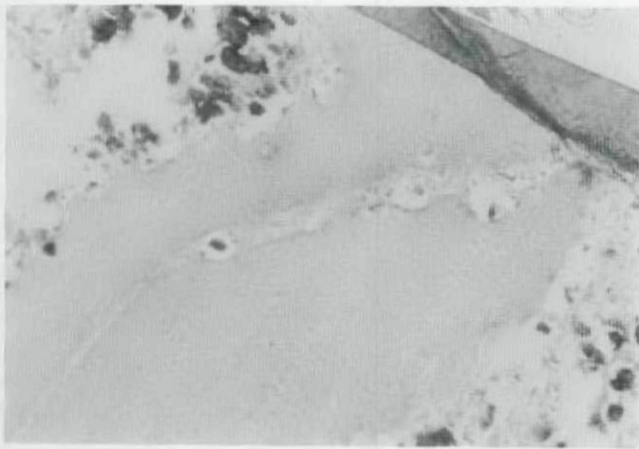


FIG. 6. The transepidermal channel containing calcium is easily demonstrated in this histopathologic section from a perforating calcified nodule. (X100). (Courtesy of Dennis A. Weigand, M.D.)

the epithelium, with tongues of epithelium surrounding and engulfing the bacterial and protozoal organisms, respectively. They were then seen to be eliminated through a transepidermal channel to the surface. It has also been suggested that TE of fungal spores (Medlar bodies) may occur as a regular phenomenon in cutaneous chromomycosis.<sup>45,46</sup>

### Transepithelial Elimination of Nevocellular Nevus and Malignant Melanoma

The first report of a nevus exhibiting the phenomenon of TE was reported by Rupec,<sup>47</sup> who described a large series of junctional nevocellular nevi in which TE of junctional nests could be demonstrated in 8 of 65 lesions. Later, Rupec et al.<sup>48</sup> reported a similar large series of 52 female and 18 male patients, aged 2-49 years, with benign juvenile melanoma (Spitz's nevus). He found only one case with TE of Spitz's nevus cell nests in his series.

The first North American report of perforating melanoma was published by Goette,<sup>49</sup> whose 56-year-old woman patient presented with a nodular melanoma on the right calf. The epidermis in the center of the lesion was characterized by pseudoepitheliomatous hyperplasia and formed a perforating channel filled with melanoma cells. Goette did not state the incidence of TE seen in malignant melanoma but postulated that TE may be a mechanism of eliminating malignant cells from the skin, as opposed to the commonly observed epidermal erosion seen over many malignant tumors.

Gartann et al.<sup>50</sup> reviewed the phenomenon of perforating nevi and malignant melanoma in a recent article. They found that in malignant melanoma, tumor cells occurred quite frequently within the stratum corneum. In contrast, TE of nevus cells represented a very rare phenomenon that occurred in only 0.13% of active nevocellular nevi. They thought that TE of nevus cells, however, did not reflect malignant degeneration.

### Transepidermal Elimination of Calcium-containing Material

TE of calcium-containing material has been reported in several instances. Weiner, in 1952, drew attention to this phenomenon in which TE of calcium occurred in a solitary congenital nodule.<sup>51</sup> Later, Schoenfeld et al.<sup>52</sup> reported four cases of calcium deposition in the skin following electroencephalography. Histology performed in three cases showed TE of calcium via



a transepidermal or transfollicular route. An underlying mild granulomatous reaction was present in all patients.

Weigand<sup>53</sup> reported a 15-year-old black man who presented with a 3-month history of a hard, superficial, pale yellow, dome-shaped nodule, 5 mm in diameter and 2 mm high on the right infraorbital fold. Histologic examination of this lesion revealed a subepidermal calcified nodule with apparent origin in the hair follicles. Seen also on the histologic sections was the presence of calcium deposits in the upper dermis, scattered in the epidermis in an area of epithelial hyperplasia and in the stratum corneum. The progression of dermal calcium deposits in an ascending fashion through the epidermis suggested TE. Eng and Mandrea, in 1961,<sup>54</sup> described two children who presented with milia-like lesions in the pubic and groin area. Biopsy of these lesions showed TE of calcium deposits perforating through the epidermis, with the surrounding epithelium hyperplastic.

Transepidermal elimination of idiopathic primary cutaneous ossification or osteoma cutis has been reported mostly in the French literature. Several cases demonstrated TE of bony fragments on histologic examination, with formation of hyperplastic tongues of epidermis surrounding a focus of bony fragments. Subsequent engulfment resulted in transportation and elimination of these fragments from the dermis.<sup>55-57</sup>

### Perforating Porokeratosis of Mibelli

Porokeratosis of Mibelli is a distinct genodermatosis consisting of a plaque with a raised border containing a central furrow, the coronoid lamellae. The entity of perforating porokeratosis of Mibelli is in dispute; only two reports have described this entity thus far.<sup>58,59</sup> These reports present a 51- and a 68-year-old woman with classical lesions of porokeratosis of Mibelli with no clinical suggestion of a perforating disorder. Biopsy specimens from both patients revealed the coronoid lamellae in opposition to the dermis, the normally intervening basal cells being absent in some areas. On biopsy, one patient also demonstrated the presence of amorphous material that extended from the dermis, through the breach in the epidermis, and upward to the surface.<sup>58</sup> Masson's trichrome stain confirmed that the perforating material was collagen.

### Miscellaneous Conditions

The exact nosologic position of the following entities is uncertain at this time but mention should be

given in this discussion of disorders of TE. Bovenmeyer<sup>60</sup> reported TE of eruptive vellus hair cysts in a 9-year-old who had multiple, asymptomatic umbilicated flesh-colored papules on the sternal area. Hyland and Kheir<sup>61</sup> described a patient with long-standing hidradenitis suppurativa in whom biopsy of the sinus tracts and ulcers showed TE of abnormal elastic tissue (a histologic finding initially thought to be specific for EPS). Their patient differed from EPS because of the absence of the typical clinical and histologic picture of EPS.

Although traditionally thought of as primary disorders of transepithelial elimination,<sup>62</sup> perforating folliculitis and Kyrle's disease are not disorders of TE in the strictest sense. Perforating folliculitis was first described in 1968<sup>63</sup> and was immediately recognized as a common disorder. The clinical appearance consists of multiple erythematous papules, 2-8 mm in diameter, with a central keratinous plug that can be removed easily. Papules are almost always follicular and do not coalesce. Distribution of lesions are limited to the arms, thighs, and buttocks. The histology centers around a curled hair that is almost always present (serial section must be performed). The hair may induce areas of rupture of the infundibular epithelium into the dermis. At the sites of rupture, a focal inflammatory infiltrate containing altered collagen and elastic fibers (that have lost their orceinophilic staining properties and therefore stain brightly eosinophilic) can be seen. This focus of inflammation and degeneration is then surrounded by reactive proliferating follicular epithelium and is thus moved upward into the follicular cavity and eventually eliminated. Since the initial event is rupture and release of irritating follicular contents into the dermis, and not primary elimination of abnormal connective tissue components or foreign bodies, this disease should not be considered a primary disorder of TE.<sup>64</sup>

Kyrle's disease was first described in 1916<sup>65</sup> in a healthy 22-year-old white woman with asymptomatic, generalized, papular eruption located primarily on the extremities. Kyrle termed this new disorder "hyperkeratosis follicularis et parafollicularis in cutem penetrans." Early lesions are pin head size with a silvery scale. Subsequent enlargement to a 3-4-mm hyperkeratotic papule with a central, large cone-shaped plug occurs. Location is both follicular and perifollicular and lesions can appear as confluent polycyclic plaques when on the extremities. Constantine and Carter<sup>66,67</sup> reviewed the literature and excluded many reported cases of Kyrle's on the basis of strict clinical and histologic criteria. They used the

following clinical criteria: (1) chronic, scattered, generalized, papular eruption with hyperkeratotic cone-shaped plugs; (2) lesions are both follicular and perifollicular; (3) lesions may coalesce into hyperkeratotic verrucous plaques; and (4) lesions are not present on the palms and soles and do not involve the mucous membranes. In addition, their cases had to satisfy rigid histologic criteria, including: (1) a hyperkeratotic plug filling an epithelial invagination; (2) parakeratosis within the plug; (3) basophilic cellular debris (not staining with elastic tissue stains) within the plug; and (4) parakeratotic or abnormal keratinization of all the epidermal cells, including the basal cells, in at least one region deep to the plug. In this region, epidermal disruption occurred, resulting in a foci of keratinized cells in the dermis, producing a granulomatous reaction. Kyrle's disease differs from perforating folliculitis by its rarity, the presence of a perifollicular location, and ability to coalesce into verrucous plaques—features that are absent in perforating folliculitis. Furthermore Kyrle's disease is thought to be a defect in the keratinization process, which composes the keratotic plug.<sup>67</sup> This may be the result of a clone of abnormal cells that may proliferate at a faster rate than the adjacent normal keratinocytes. Abnormal growth results in premature and abnormal keratinization within the clone. In the majority of cases this is followed by disruption of the epidermis into the dermis with the release of highly irritating keratin. The presence of this foreign material evokes a granulomatous foreign body reaction. Therefore, since the initial pathogenic event in Kyrle's appears to be an epidermal mutant clone with subsequent introduction of irritant material into the dermis, this, along with perforating folliculitis, appears not to be a disorder of TE. Furthermore, Mehregan considers most if not all cases of Kyrle's disease to be cases of perforating folliculitis.<sup>68</sup>

### Experimental Evidence

Transepidermal elimination was studied extensively by Bayoumi et al.,<sup>69</sup> who injected charcoal particles subepidermally into guinea pig flank skin. Elimination of the particles via the epidermis occurred in 4 days. Histologically, the hair follicles became hyperplastic and at times participated in the phenomenon with transfollicular elimination. They noted that this reaction had some similarities to experimental wound healing and concluded that TE would occur only if the offending material was neither strongly irritant (which would cause epidermal necrosis) nor com-

pletely nonirritative (or else there would be no dermal reaction). Furthermore, they concluded that: (1) the most "sensitive" zone was located above the level of the hair papillae in the dermis; (2) increased epidermal mitotic activity and active epidermal cell movement were involved in the response; and (3) the material was expelled via the hair follicle or intact epidermis.

Later in 1980, Bayoumi and Marks<sup>70</sup> used the guinea pig model and skin explants further to define various parameters involved in transepithelial elimination. Using various drugs, such as chlorpheniramine, cimetidine, indomethacin, and various combinations, they found that none of the drugs administered to the animals had any effect in preventing the development of TE. Indomethacin, however, diminished the epidermal hyperplasia but did not alter the basic process. Skin organ studies showed that the initiation and development of TE was dependent on the test site being *in situ* in the animal; however, it was also apparent that one initiated, TE would continue unabated even *in vitro*. TE occurred at all the anatomic sites tested except the tongue, implying that TE is a fundamental epithelial response and not tied to a particular type of epidermal maturation or differentiation. They concluded that TE is not initiated by the release of histamines nor prostaglandins, although the associated hyperplasia may be partially prostaglandin-dependent.<sup>70</sup> Also, physical distortion of the tissue architecture of the skin may be implicated in the pathogenesis.

### Conclusion

Dermal-epidermal interactions have become of paramount importance in the field of dermatology. It has become clear that dermal stimuli profoundly affect the behavior of the overlying epidermis; numerous examples can be found in the literature. Mehregan<sup>71</sup> has pointed out three types of epidermal reaction to foreign material in the dermis. First, an inert material such as hemosiderin will evoke minimal or no inflammatory response and therefore little or no epidermal reaction. Second, a strongly irritant body will evoke a maximal inflammatory and/or granulomatous response and, if the reaction is superficial enough, the subsequent tissue destruction will lead to necrosis and epidermal degeneration. Third, the subject of this article, is the phenomenon of transepidermal elimination. TE is a fascinating example of dermal-induced epidermal reactive phenomenon in which there is a purposeful epidermal response to

eliminate the foreign or altered body. This expulsion of particulate matter from the dermis into the exterior is probably mediated by a complex series of interrelated events. The first event may involve recognition of a foreign body by uncharacterized receptors.<sup>70</sup> Recognition may be followed by the elaboration of a substance by dermal components, which induces hyperproliferation of the epidermis. The resultant formation of perforating channels requires the coordination of activities such as enhanced epidermal growth, cell movement, and phagocytosis by individual epidermal cells.<sup>70</sup> TE may occur as the basic pathologic event in disorders such as elastosis perforans serpiginosa and reactive perforating collagenosis or as a secondary reactive process in dermatoses such as granuloma annulare and pseudoxanthoma elasticum.

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### Drug Names

Isotretinoin: Accutane  
penicillamine: Cuprimine, Depen  
tretinoin: Retin-A

### References

- Hazelrigg DE. Generalized perforating granuloma annulare. *Cutis*. 1979;23:813-814.
- Bauman WE. Disseminated perforating granuloma annulare. *Int J Dermatol*. 1979;18:415-416.
- Aliaga A, Serrano G, de la Cuadra J, et al. Perforating granuloma annulare and vitamin D. *Dermatologica*. 1982;164:62-66.
- Dick DC, Syme IG. Perforating granuloma annulare and scleritis. *Arch Dermatol*. 1982;118:67-68.
- Pinkus H. Über atypische tuberkulide: Zugleich ein Beitrag zuratiologie des granuloma annulare. *Arch Dermatol Syphilol*. 1934;170:194.
- Civatte DA. Les formes tuberculo-ulcereuses et tuberculogommeuses du granulome annulaire. *Ann Dermatol Syphilol*. 1952;79:387-397.
- Calnan CD. Granuloma annulare. *Br J Dermatol*. 1954;66:254.
- Owens DW, Freeman RG. Perforating granuloma annulare. *Arch Dermatol*. 1971;103:64-67.
- Van der Meer JB, Bos WH, Van der Putte SCJ. Perforating granuloma annulare. Proc. 214th Meet. of the Netherland's Society of Dermatologists, Utrecht 1978. *Br J Dermatol*. 1979;101:219-220.
- Jacyk WK, Birecka I. Generalized perforating granuloma annulare. *Arch Dermatol*. 1974;110:809.
- Tan R. Perforating granuloma annulare. *Br J Dermatol*. 1977;97:51-52.
- Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol*. 1980;3:217-230.
- Duncan WC, Smith JD, Knox JM. Generalized perforating granuloma annulare. *Arch Dermatol*. 1973;108:570-572.
- Izumi AK. Generalized perforating granuloma annulare. *Arch Dermatol*. 1973;108:708-709.
- Smith JD, Goette DK. Perforating granuloma annulare. *South Med J* 1977;70:499-501.
- Delaney TS, Gold SC, Leppard B. Disseminated perforating granuloma annulare. *Br J Dermatol*. 1973;89:523-526.
- Bardach H. Granuloma annulare with transfollicular perforation. *J Cutan Pathol*. 1977;4:99-104.
- Bardach H. Granuloma annulare with follicular perforation. *Dermatologica*. 1982;165:47-53.
- Agren-Jonsson S, Holst R, Dahlquist I. Perforating granuloma annulare: Report of three cases from Scandinavia. *Acta Dermatologica Venereol (Stockh)*. 1977;57:543-546.
- Bard JW. Chondrodermatitis nodularis chronica hellicis. *Dermatologica*. 1981;163:376-384.
- Carton FX, Denceux JP, Gonthier MF, et al. Granulome annulaire perforant. *Bull Soc Fr Dermatol Syphilol*. 1976;83:217-219.
- Buechner SA, Winkelman RK, Banks PM. Identification of T-cell subpopulations in granuloma annulare. *Arch Dermatol* 1983;119:125-128.
- Gattlen JM, Delacretaz J. Le granulome annulaire perforant. *Dermatologica*. 1975;151:368-375.
- Batres E, Klima M, Tschen J. Transepithelial elimination in cutaneous sarcoidosis. *J Cutan Pathol*. 1982;9:50-54.
- Schutt DA. Pseudoxanthoma elasticum and elastosis perforans serpiginosa. *Arch Dermatol*. 1965;91:151-152.
- Lund HZ, Gilbert CF. Perforating pseudoxanthoma elasticum: Its distinction from elastosis perforans serpiginosa. *Arch Pathol Lab Med*. 1976;100:544-546.
- Smith EW, Malak JA, Goodman RM, et al. Reactive perforating elastosis: a feature of certain genetic disorders. *Johns Hopkins Med J*. 1962;111:235-251.
- Premalatha S, Yesudian P, Thambiah AS. Periumbilical pseudoxanthoma elasticum with transepidermal elimination. *Int J Dermatol*. 1982;10:604-605.
- Hicks J, Carpenter CL, Reed RJ. Periumbilical perforating pseudoxanthoma elasticum. *Arch Dermatol*. 1979;115:300-303.
- Bos WH. Pseudoxanthoma elasticum associated with perforating elastoma. *Dermatologica*. 1968;136:296-297.
- Pai SH, Zak FG. Concurrence of pseudoxanthoma elasticum, elastosis perforans serpiginosa and systemic sclerosis. *Dermatologica*. 1970;140:54-59.
- Caro I, Sher MA, Rippez JJ. Pseudoxanthoma elasticum and elastosis perforans serpiginosa. Report of two cases. *Dermatologica*. 1975;150:36-42.
- Schwartz RA, Richfield DF. Pseudoxanthoma elasticum with transepidermal elimination. *Arch Dermatol*. 1978;114:279-280.
- El Mofty AM, El Enany G. Kyrle's disease and elastosis perforans serpiginosa. *Int J Dermatol*. 1974;13:119-123.
- Graham JH, Hunter GA. Perforating pseudoxanthoma elasticum. *Arch Dermatol*. 1976;112:1781.
- Pope FM. Two types of autosomal recessive pseudoxanthoma elasticum. *Arch Dermatol* 1974;110:209-212.
- Domonkos AN. Pseudoxanthoma elasticum. *Arch Dermatol*. 1968;98:551-552.
- Bardach H. Perforating lichen nitidus. *J Cutan Pathol* 1981;8:111-116.
- Bard JW. Transepithelial elimination in popular mucinosis. *Arch Dermatol*. 1983;119:95-97.
- Horn RT, Goete DK. Perforating rheumatoid nodule. *Arch Dermatol*. 1982;118:696-697.
- Parra CA. Transepithelial elimination in necrobiosis lipoidica. *Br J Dermatol*. 1977;96:83-86.

42. Garcia E, Silva L, Capitaio-Mor M, et al. Necrobiose lipidique perforante. *Ann Dermatol Venereol*. 1981;108:891-896.
43. Goette DK. Transepithelial elimination in botryomycosis. *Int J Dermatol*. 1981;20:198-200.
44. Wood MG, Srolovitz H, Schetman D. Schistosomiasis: Paraplegia and ectopic skin lesions as admission symptoms. *Arch Dermatol*. 1976;112:690-695.
45. Batres E, Wolf JE, Rudolph AH, et al. Transepithelial elimination of cutaneous chromomycosis. *Arch Dermatol*. 1978;114:1231-1232.
46. Zaias N, Rebell G. A simplified and accurate diagnostic method in chromoblastomycosis. *Arch Dermatol*. 1973;108:545-546.
47. Rupec M, Vakilzadeh Zur frage der transepidermalen ausscheidung von navuszellnestern. *Dermatologica*. 1974;148:61-64.
48. Rupec M, Kint A, Horn W. Das juvenile melanom. *Hautarzt*. 1979;30:581-585.
49. Goette DK. Transepithelial elimination in malignant melanoma. *J Assoc Milit Dermatol*. 1980;6:9.
50. Gartmann H. Transepidermale ausscheidung von navus-und melanomzellen. *Hautarzt*. 1982;33:495-497.
51. Winer LH. Solitary congenital nodular calcification of the skin. *Arch Dermatol*. 1952;66:204-211.
52. Schoenfeld RJ, Grekin JN, Mehregan A. Calcium deposition in the skin: A report of four cases following encephalography. *Neurology*. 1965;15:477-480.
53. Weigand DA. Subepidermal calcified nodule. Report of a case with apparent hair follicle origin. *J Cutan Pathol*. 1976;3:109-115.
54. Eng AN, Mandrea E. Perforating calcinosis cutis presenting as milia. *J Cutan Pathol*. 1981;8:247-250.
55. DuPerrat B, Vanbremeersch F. Osteome perforant verruciforme post-traumatique. *Ann Dermatol Sympilol (Paris)*. 1963;1:37-39.
56. Laugier P. Calculs cutanes perforants verruciformes. *Ann Dermatol Venereol*. 1977;104:893-895.
57. Delacretaz J, Koenig R. Osteome perforant dans le cadre d'une osteomatose regionale acquise. *Dermatologica*. 1978;156:251-254.
58. Izumi AK. Perforating porokeratosis of mibelli. *Cutis*. 1981;28:45-46.
59. Witkowski JA, Wood MG. Porokeratosis of Mibelli: A perforating disease of the epidermis. *Cutis* 1982;29:171-186.
60. Bovenmeyer DA. Eruptive vellus hair cysts. *Arch Dermatol*. 1979;115:338-339.
61. Hyland CH, Kheir SM. Follicular occlusion disease with elimination of abnormal elastic tissue. *Arch Dermatol*. 1980;116:925-928.
62. Lever WF, Schaumburg-Lever G. *Histopathology of the skin*. 6th ed. Philadelphia: JB Lippincott 1983;273-276.
63. Mehregan AH, Coskey RJ. Perforating folliculitis. *Arch Dermatol*. 1968;97:394-399.
64. Burkhart C. Perforating folliculitis: A reappraisal of its pathogenesis. *Int J Dermatol*. 1981;20:597-599.
65. Kyrle J. Hyperkeratosis follicularis et parafollicularis in cutem penetrans. *Arch Dermatol*. 1916;123:466-493.
66. Carter VH, Constantine VS. Kyrle's disease. I. Clinical findings in five cases and review of the literature. *Arch Dermatol*. 1968;97:624-632.
67. Constantine VS, Carter VH. Kyrle's disease. II. Histopathologic findings in five cases and review of the literature. *Arch Dermatol*. 1968;97:633-639.
68. Pinkus H, Mehregan AH. *A guide to dermatohistopathology*. 3rd ed. New York: Appleton-Century-Crofts, 1981;209.
69. Bayoumi AH, Gaskell S, Marks R. Development of a model for transepidermal elimination. *Br J Dermatol*. 1978;99:611-620.
70. Bayoumi AHM, Marks R. Transepidermal elimination: Studies with an animal model. *Br J Exp Pathol*. 1980;61:560-566.
71. Mehregan AH. Elastosis perforans serpiginosa: a review of the literature and report of 11 cases. *Arch Dermatol*. 1968;97:381-393.

### Synthetic Dyes and Drug Entities

We have seen the development of a synthetic dye industry and its removal from England to Germany and, to a lesser extent, to Switzerland. By accident, or by empirical chemistry, a number of pure organics had been synthesized; some had recently been found to be medicinally useful. These findings too were empirical.

Several examples of such compounds will be noted here. Chloral had been prepared by Liebig in 1831, but was only introduced to medicine in 1869, when it was used by Oscar Liebrich (1939-1908) as a hypnotic. Acetylsalicylic acid (ASA) was first prepared in 1859 by Gilm, more than three decades after salicylic acid had been obtained by oxidation of salicin's aglycone. It was not until the mid 1870's that salicylates were shown to be antirheumatics and it would not be until 1898-99 that the acetyl derivative of salicylic acid would be resynthesized by Dresser and introduced to medicine as Aspirin. These two examples are chosen deliberately for another reason: to illustrate German use of the British patent system.

Chloral and ASA are both subjects of patent applications by British agents acting for German subjects and interest, e.g. Liebrich as an individual in the Chloral patent; Dresser in the case of ASA assigning his interest to his employers. Liebrich's claim was for "the application and use of chloral or hydrate of chloral, or trichloroacetic acids or salts or compounds of the same for the purpose of producing anaesthesia". Strangely he did not include trichloroethanol in his claim.—*Paterson GH. Synthetic dyes and drug entities. Canad Bull Med Hist*. 1984;1:11-13.

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