"Hidradenitis suppurativa" is acne inversa! An appeal to (finally) abandon a misnomer

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Abstract
The term “hidradenitis suppurativa” is firmly entrenched in the dermatological literature although it refers to a false pathogenetic concept. The term was historically coined based merely on the characteristic distribution of the apocrine glands and the anatomical coincidence with the disease process. At center stage is not a suppurative inflammation of the apocrine sweat glands but an occlusion of the hair follicles, comparable to acne vulgaris. Reviewing the literature on this subject, we were astonished to find that even articles that concluded that the entity represents a form of follicular occlusion still referred to it as hidradenitis suppurativa. The disorder shares histopathological and clinical aspects with acne vulgaris modified under the special circumstances of anatomical regions rich in apocrine glands. It is acne inversa because, in contrast to acne vulgaris, the disease involves intertriginous localizations and not the regions classically affected by acne. We suggest that the term “hidradenitis suppurativa” for this disease should (finally) be abandoned in favour of “acne inversa.”

Introduction
The term “hidradenitis suppurativa” implies erroneously that the primary pathogenetic event is centered upon the (apocrine) sweat glands, a thesis discredited over the past 50 years. Our study herein demonstrates the basic pathologic processes involved in this entity and will affirm our support for a long overdue name change.

The Evolution of the Term “Hidradenitis suppurativa”

The introduction of the term “hidradenitis suppurativa” in the medical literature was purely based on clinical speculation. In 1833, Purkinje discovered the sweat glands in human skin (quoted by Gordon). In the same year, the French physician Velpeau reported a peculiar inflammatory process characterized by superficial abscess formation in the axillae, under the breasts and in the genital and perianal areas. Shortly thereafter, in 1845, Robin, a French anatomist, published a paper on the structure and location of the sweat glands in the axilla. (However, it was not until 1922 that the German anatomist Schiefferdecker classified and divided the sweat glands into the two categories that he named apocrine and eccrine.) In the light of Robin’s observation, it was again a French physician, the surgeon Verneuil, who in 1854 related the inflammation to the sweat glands and in 1865 coined the term “hidrosadénite phlegmoneuse”, the French term for hidradenitis suppurativa. Without performing histological studies, Verneuil viewed the entity he reported as a disorder of the sweat glands based merely on the characteristic distribution of the apocrine glands and the anatomical coincidence with the disease process.

“I make this observation only with reservations, for it is chiefly the curious distribution of these collections that made me adopt the interpretation which I give here. It is therefore a point to be restudied and to be demonstrated in a more satisfactory manner.”

(Verneuil, 1854, quoted in translation by Lane)

His conclusion was thus speculative in nature.

One of the first detailed histopathological studies was that by Brunsting. In his paper published in 1939, he considered the primary involvement of the apocrine glands as the essential histological feature of “hidradenitis suppurativa.” More than a decade later, Kierland, at the Mayo Clinic in Rochester, MN, also reported histopathological observations. He emphasized that the earliest infiltrate in “hidradenitis suppurativa” would involve the lumina of the apocrine glands and the surrounding periglandular tissue.

An Experimental Model for “Hidradenitis suppurativa” and its Opponents

Probably the most lasting impact on the subsequent continued perception of “hidradenitis suppurativa” as a primary...
inflammatory process of the apocrine glands was produced by an experimental paper by Shelley and Cahn in 1955.\textsuperscript{10} The authors applied perforated belladonna adhesive tape to manually depilated axillary skin and were able to evoke lesions at the tape side clinically resembling “hidradenitis suppurativa” in three out of 12 volunteers. Histologically they observed plugging and dilatation of the apocrine sweat duct associated with severe inflammation limited to a single apocrine sweat gland. The adjacent glands, not exhibiting an occluded ductal orifice, however, were entirely normal as were the hair follicles, sebaceous glands and eccrine glands. Shelley and Cahn\textsuperscript{10} concluded that “hidradenitis suppurativa” fundamentally represented a bacterial infection of an obstructed apocrine sweat gland with the causative bacteria deriving from the normal surface flora.

On the basis of this study by Shelley and Cahn, many subsequent articles, some quite recent, have portrayed “hidradenitis suppurativa” primarily as a disorder of the apocrine glands,\textsuperscript{11–19} despite early concerns that this might not be the case. Criticism of their experimental model of “hidradenitis suppurativa” was voiced as early as 1957, shortly after Shelley and Cahn\textsuperscript{10} published their paper. Early opposition came from the Chicago dermatologist Tibor Benedek,\textsuperscript{19} who expressed his doubts in no uncertain terms:

“\textit{A more poorly conceived experiment for the reproduction of a skin disease than the foregoing [Shelley and Cahn’s] is hard to imagine. This so-called experimental reproduction of h.s. [hidradenitis suppurativa] in man bears no similarity to the spontaneously developed disease, either clinically, histopathologically or bacteriologically.}”\textsuperscript{19}

Although Benedek was right in that he interpreted the involvement of the apocrine glands as only secondary, he thought at the time that the pathologic process started in the periglandular connective tissue and that the hair follicle was not central to the pathogenetic events taking place in “hidradenitis suppurativa”. Instead, he postulated that a “hematogen-endogenous inflammatory reaction to hyper-sensitivity towards … [a] pathogenic bacterium” played a causative role in the disease process.\textsuperscript{20} It has since been documented repeatedly that bacterial invasion is only a secondary phenomenon and does not play a major role in “hidradenitis suppurativa”\textsuperscript{21–22}.

Further criticism of Shelley and Cahn’s experimental model was voiced years later by Yu and Cook,\textsuperscript{23} who argued that it might not be an accurate model for “hidradenitis suppurativa” for a number of reasons. They pointed out that the traumatic procedure of manual depilation may have produced changes in the tissue, in the same way that shaving skin with a safety razor has been shown to predispose to infection.\textsuperscript{24} Furthermore, they did not regard the addition of atropine to the tape as simulation of a physiological process and additionally pointed out that only 25\% of the subjects developed lesions clinically resembling hidradenitis suppurativa. Yu and Cook\textsuperscript{23} also referred to their own histopathological studies. They observed neither keratinous plugging of dilated apocrine ducts nor inflammation confined to a single sweat gland unit in specimens from patients with “hidradenitis suppurativa”. These changes, however, were the histopathological alterations regarded by Shelley and Cahn\textsuperscript{10} as playing the central role in the pathogenesis of the disease.

An additional argument against Shelley and Cahn’s experimental model came from Edlich et al.\textsuperscript{25} They argued that it has not been proven that the lesions described by Shelley and Cahn progress to the chronic condition recognized as “hidradenitis suppurativa” clinically.

### A Shift in Paradigm: “Hidradenitis suppurativa” as a Disorder of the Hair Follicle rather than the Apocrine Gland

Even before Shelley and Cahn’s experimental model was published, one of the first authors to depart from the concept of a primary involvement of the apocrine glands in “hidradenitis suppurativa” was Brunsting. Although in 1939 he still viewed inflammation of the sweat glands as the main pathogenetic event,\textsuperscript{1} in a follow-up publication in 1952 he proposed a relationship to acne.\textsuperscript{26} Brunsting based his changed perspective on his observation that the earliest histopathological changes consist of a folliculitis followed by severe perifolliculitis, both typical of acne.\textsuperscript{26} The apocrine glands would only be involved by extension of the process into the deep layers of the skin.

Subsequent studies, based on detailed histopathological observations, confirmed his view.\textsuperscript{27–35} They all agreed that apocrine gland involvement is not consistently seen and does not represent the main pathogenetic event but is rather secondary in nature. They only differed in the percentage of cases in which actual involvement of the apocrine sweat glands was noted, varying between 14\%\textsuperscript{35} and 62\%.\textsuperscript{28} The earliest changes are those of follicular hyperkeratosis resulting in follicular obstruction, not unlike that seen in acne vulgaris.\textsuperscript{26–35} Spongiform infundibulofolliculitis and perifolliculitis may accompany the follicular hyperkeratosis.\textsuperscript{35} Sweat gland involvement, however, is encountered only after the dilated hair follicle ruptures, secondary bacterial colonization ensues and the inflammation extends into the surrounding tissue.\textsuperscript{28}

### Commentary: Own Histopathological Observations

The following observations are based on the histopathological analysis of 176 specimens of “hidradenitis suppurativa” from 152 patients: 116 were female (average age 35.9 years) and 36 were male (average age: 40.5 years). The majority of the specimens were from either the axillae or the inguinal areas.
Sellheyer and Krah"Hidradenitis suppurativa' is acne inversa! Review

Figure 1 The early stage is characterized by comedo formation (arrowhead). Note that the apocrine glands are unremarkable (arrow). Sections were stained with hematoxylin-eosin; magnification: ×13

Figure 2 (a) Continuing dilatation of the follicular infundibulum leads to rupture into the surrounding dermis evoking an acute inflammatory infiltrate (arrowhead). The apocrine glands (arrows) are not involved. (b) Higher magnification of ruptured comedo. (c) Site of rupture (arrow) in another comedo. Sections were stained with hematoxylin-eosin; magnification: (a) ×4; (b) ×13; (c) ×165

Figure 3 (a) Over time, a granulomatous infiltrate (arrows) replaces the neutrophilic infiltrate and the process may remain confined. (b) Higher magnification of granulomatous infiltrate. Sections were stained with hematoxylin-eosin; magnification: (a) ×14; (b) ×162

Figure 4 (a) An abscess develops, if the inflammation following rupture of the comedo is more florid. Note that the apocrine glands are not involved (arrow). (b) Higher magnification of apocrine glands (arrow) in (a). Sections were stained with hematoxylin-eosin; magnification: (a) ×21; (b) ×83

Figure 5 (a) Only if the inflammation spreads further do the apocrine glands become involved (arrow). (b) Then, neutrophils invade the glandular lumina (arrow) and the glands are destroyed. Sections were stained with hematoxylin-eosin; magnification: (a) ×21; (b) ×83

Figure 6 Naked hair shafts may be the only indication that the process started from the hair follicle. Sections were stained with hematoxylin-eosin; magnification: ×42

Figure 7 Sinus tracts are a late sign of the disease. Sections were stained with hematoxylin-eosin; magnification: ×4

Figure 8 When they rupture, the disorder enters a vicious cycle. Sections were stained with hematoxylin-eosin; magnification: ×13
The disease process starts with follicular hyperkeratosis and dilatation of the follicular infundibula evolving into comedones, comparable to those observed in acne vulgaris (Fig. 1). At this time, the apocrine glands are not involved. Eventually the dilated follicular infundibulum ruptures, typically at the lower portion, and the content spills into the surrounding dermis, evoking an acute inflammatory response in the immediate vicinity of the rupture site (Fig. 2a–c). Again, the apocrine glands do not show any signs of involvement nor an indication that they are the anatomical starting point of the sequence of events. If the inflammation remains confined to the immediate vicinity of the hair follicle, over time the initially neutrophilic infiltrate subsides and is gradually replaced by a granulomatous one, often with the addition of multinucleated foreign body giant cells (Fig. 3a–b). If, however, the acute inflammatory response following rupture is more florid, a large abscess develops which may extend into the subcutaneous tissue (Fig. 4a). Apocrine glands near the abscess, but not involved by it, are unremarkable (Fig. 4b). Apocrinitis only evolves by extension of the inflammatory process, leading to destruction of apocrine glands (Fig. 5a–b). Apocrine glands located further away from the extending abscess are morphologically unremarkable. When extensive tissue destruction has ensued, naked hair shafts, surrounded by an inflammatory infiltrate, are often the only indication that the process started from the hair follicle (Fig. 6).

In an attempt of the tissue to confine the inflammatory reaction and to prevent further spread, remnants of the hair follicle epithelium proliferate and sinus tracts form, often surrounded by fibrosis (Fig. 7). The sinus tracts communicate with the surface. Upon bacterial superinfection, they rupture and the process becomes self-maintaining and enters into a vicious cycle (Fig. 8). Sinus tract formation is the main reason for the chronicity of the disease and why surgery is the only therapeutic option capable of achieving a long-lasting cure. This is necessary in order to successfully eradicate the frequently extensive sinus tracts that are responsible for the chronicity of the disease. This sequence of events led us to our appeal.

Discussion

We have demonstrated, based on histopathological observations reported in the literature and on our own observations, that the term “hidradenitis suppurativa” is a misnomer. The central pathogenetic event is not a suppurative inflammation of the apocrine glands but an occlusion of the hair follicles. This also explains the clinical observations that comedones are a part of the initial presentation and that isotretinoin and acitretin are therapeutically effective, at least in the very early stages or as adjunctive measures. In 1956, Pillsbury, Shelley and Kligman introduced the term “follicular occlusion triad” as an umbrella term for “hidradenitis suppurativa”, dissecting cellulitis of the scalp, and acne conglobata. In 1975, Plewig and Kligman added the pilonidal sinus as the fourth component of the ensemble and changed the name to “acne tetrad”. Histopathologically, all four entities are identical and share the same pathogenetic mechanism with acne vulgaris: follicular occlusion. Whereas acne vulgaris, however, involves the anatomical areas rich in sebaceous glands (the face, upper back and upper chest), all four components of “acne tetrad” affect inverse anatomical areas. Dissecting cellulitis involves the scalp. Acne conglobata extends often to the upper arms and thighs, neck, retroauricular area, abdomen and buttocks. Pilonidal sinus is located in the presacral area. “Hidradenitis suppurativa” most commonly affects axillae, inguinal and perineal areas. Because of these inverse localizations of the components of acne tetrad, Plewig and Steger in 1989 suggested the term “acne inversa” instead. The term “acne inversa” honors only the common pathogenetic relationship of its four different expressions to acne. The term “acne inversa” not only links the pathogenesis of its four facets to acne but additionally reflects the fact that they are an expression of follicular occlusion in localizations inverse to acne vulgaris.

When the histopathology, clinical presentation and some of the therapeutic aspects of “hidradenitis suppurativa” are those of acne (modified under the special circumstances of anatomical regions rich in apocrine glands), why not call it as such and abandon the misnomer? It is acne inversa because, in contrast to acne vulgaris, the disease involves ectopic (intertriginous) localizations and not the regions classically affected by acne vulgaris.

In conclusion, the term “hidradenitis suppurativa” should be abandoned. “Hidradenitis suppurativa” is acne inversa!

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