What causes hidradenitis suppurativa?


Abstract: Hidradenitis suppurativa (HS) – a rather common, very chronic and debilitating inflammatory skin appendage disorder with a notoriously underestimated burden of disease – has long been a playground for the high priests of nomenclature: Ask a bunch of eminent dermatologists and skin pathologists to publicly share their thoughts on what causes HS, and they will soon get entrenched in a heated debate on whether this historical term is a despicable misnomer. Fortunately, the recently founded Hidradenitis Suppurativa Foundation (HSF; http://www.hs-foundation.org), to which EXP DERMATOL serves as home journal, has broken with this unproductive tradition and has encouraged publication of the current CONTROVERSIES feature. This is exclusively devoted to discussing the pathobiology of this chronic neutrophilic folliculitis of unknown origin. Although traces of terminological bickering remain visible, it does the HS experts in our virtual debate room credit that they engage in a constructive and comprehensive dissection of potential pathogenesis pathways that may culminate in the clinical picture we know under the competing terms HS or acne inversa. These experts sketch more often complementary than mutually exclusive pathogenesis scenarios, and the outlines of a conceivable consensus on the many open pathobiology questions begin to emerge in these CONTROVERSIES. Hopefully, this heralds a welcome new tradition: to get to the molecular heart of HS pathogenesis, which can only be achieved by a renaissance of solid basic HS research, as the key to developing more effective HS therapy.

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Prelude

Apocrine or not, that is the question…

In the context of HS, it has become foolhardy to speak of apocrine sweat glands ever since pathologists have demonstrated that the primary histological event was in the follicular duct, like in acne. It was then simple, if not to say simplistic, for many dermatologists to forget any major differences between acne and HS, and to rename the disease ‘acne inversa’, thus replacing one possible misnomer (HS) with another – and leading investigators to a dead end, and practitioners to use ineffective treatments.

Any hypothesis about HS must take two paradoxons into account:

1 Hidradenitis suppurativa lesions have a very specific topography which is a copy of the anatomical distribution of apocrine sweat glands: axillae and groin as the main areas; breast, perineum and buttocks as accessory regions. Yet apocrine glands are not the primary target of the pathological process.

2 Hidradenitis suppurativa is not primarily an infectious disease, and yet drugs that are conducive to infection, such as corticosteroids, immunosuppressive drugs and/or anti-TNF agents, may improve the disease.

One of the most useful drug regimens in cases of active inflammatory lesions is a combination of two antibiotics: rifadin and clindamycin (1).

Paradoxon 1

The topography of involvement may be explained by two – not mutually exclusive – hypotheses: (a) the distribution of apocrine glands; and (b) shearing forces, which originate in large skin folds, especially of overweight patients.

Obesity and overweight are frequent in HS and could be a risk factor (2). However, HS is not infrequent in intermammary folds and on the buttocks, where such shearing forces are absent. Moreover, individuals with low or normal body mass index also do develop HS. Thus, while obesity and overweight are strongly associated with severity in HS, they are insufficient to explain the specific topography of the disease.

So, what about apocrine sweat glands? The rejection of apocrine glands as a main factor in the pathogenesis of HS originates in the clear demonstration that they are spared...
by the initial inflammatory and destructive process. The primary event is a follicular hyperkeratosis with plugging and dilatation of the hair follicle ensuing in inflammation, abscess and sinus tract formation. Apocrine involvement appears as a secondary phenomenon resulting from the diffusion of the granulomatous inflammation in deep structures of the skin.

The mechanism by which follicular plugging occurs in acne is not known; various candidates are hypersecretion of sebum, proliferation of P. Acnes favoured by an alteration of innate immunity and/or of inflammatory reactions, and possibly several others.

Here, the specific anatomical relationship of the apocrine gland with the follicular canal has to be taken into account: In contrast to eccrine glands, whose ducts open onto the skin surface, apocrine glands empty their content into the follicular canal, just above the sebaceous gland duct. In HS, hyperseborrhoea is definitely absent but the other factors may be at work:

An abnormal secretion – excess or absence – of a substance that is present in apocrine gland secretion under physiological conditions may therefore, after all, be the triggering factor of HS! Its morphologically recognizable effect could be in the acro infundibulum of the follicle, with the responsible gland disguising itself as an innocent bystander upon histology – a perfectly masked ‘criminal’.

**Paradoxon 2**

Hidradenitis suppurativa is a disease in which numerous bacteria are present and active (3), and in which various antibiotic regimens have definitely improved the condition in patients with severe inflammatory involvement (2). Surprisingly, numerous pro-infectious drugs have also been used with good results: corticosteroids, immunosuppressive drugs, anti-tumour necrosis factor (4,5). The coexistence of these two seemingly contradictory phenomena calls for a closer look at the properties of anti bacterial molecules which play a key role in innate and acquired immunity: the so-called anti-microbial peptides (6).

They are known to exert both pro- and anti-inflammatory functions; they alarm and activate the adaptive immune system and the keratinocytes that produce them. They induce keratinocytes migration, proliferation – a role in follicular occlusion? They are part of a complex network of cytokine and chemokine production. The absence or abnormality of one of these anti-microbial peptides would be a good candidate for explaining the infectious and inflammatory features of HS. Cathelicidins and defensins are the main representatives of this family identified today. New ones, psoriasin (7), are under consideration. Some of these peptides are produced by mature keratinocytes spontaneously or after stimulation, some are produced by eccrine sweat glands, and some are prominently subject to modulation by antibiotics (7–9).

However, until now, nothing is known about anti-microbial peptides that are specifically produced in apocrine sweat glands. This is where we need to search.

**Conclusion**

Hidradenitis suppurativa is as multifactorial as any chronic disease and probably heterogeneous. Here, I have only considered the role that apocrine glands may have, a role that might well be central – no matter, how much this gland has fallen out of fashion in HS research. The role of other factors – e.g. hair follicle anatomical/structural abnormalities (highly probable at least in a subset of HS patients), the role of obesity, the role of cigarette smoking – all deserve careful exploration. Any pathogenesis scenario, however, that completely discards apocrine glands and their specific distribution as key elements in the development of HS may soon turn out to have to be discarded itself!

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**References**

Controversies in Experimental Dermatology

Viewpoint 1

The scientific mind should view things without prejudice. Hidradenitis suppurativa (HS) is a common dermatosis, which significantly affects the lives of patients and which is notoriously difficult to treat. It is a well-defined clinical entity, consisting of recurrent crops of inflammatory lesions in inverse areas (1). It looks infectious, but it is not.

The lesions are initially transient, but gradually become intransigent and associated with significant scarring. Histologically, it is a disease of the hair follicle; associated with lympho-histiocytic inflammation, granulomatous reactions, sinus tracts and scarring (2–5). It looks like acne – but it is not.

Treatment is often disappointing, and has significant negative impact on the patient’s quality of life (6–8). Anti-inflammatory, immunosuppressive, antiandrogenic, antibiotic and surgical treatments have been described as effective, although few randomized, controlled trials exist that convincingly support these claims (1,9–11).

So, what then is HS?

Disease hallmarks

One of the most obvious hallmarks of the disease is the restriction to the skin areas affected. The disease is essentially limited to inverse areas, although aberrant lesions may occur. This lead to the original proposition that apocrine glands are involved in the disease. It is good to suggest theories – but these can be rejected later.

The inverse areas are indeed rich in apocrine glands – although the overlap between HS lesions and apocrine-rich regions of the integument is not good within an affected skin territory (3). The inverse areas are, however, also characterized by skin–skin contact and subsequent shear forces affecting the skin; increased moisture and bacterial flora, all of which may play a role.

Within the affected regions, hair follicles are invariably involved (2). The deep part of the follicle appears to be involved, rather than its superficial compartments, as seen with acne affecting convex skin surfaces (12). Clinically, closed comedones are not seen.

Although a range of bacteria may be retrieved from HS lesions, these frequently appear to be sterile (13–15). Of the bacteria identified, only a small minority are recognized pathogens, and no consistent IgG response to staphylococcal antigens is found (13). Hormones are unlikely players in the pathogenesis of HS: increased sebum excretion and other signs of cutaneous virilization are not seen, although single cases have been published to suggest this (16–19).

Similarly, the use of depilatories and other cosmetics are not associated with the disease (20,21). Scarring is prominent, but often overlooked in this disease. The fully developed disease is characterized by significant scarring and may cause contractures, and far-reaching sinus tracts, the latter often growing in a pseudo-invasive manner into the surrounding tissue.

Aetiology

The wide range of clinical HS presentations, and of occasionally successful HS treatments, invites the speculation that HS aetiology does not arise from a single external factor, but rather represents a reaction pattern within the afflicted patient. This concept is supported by genetic observations (22,23).

The effectiveness of antimicrobial drugs such as clindamycin suggest that bacteria may occasionally be responsible for starting the process (9,11). Similarly, the use of anti-inflammatory treatment such as corticosteroids or TNF-blockers, suggest a role for the immune system (24), while tobacco or physical trauma (described in convincing individual cases or epidemiological studies as trigger or aggravation factors) suggest that these factors may be involved (25). Most likely, however, they are only temporarily involved (or of secondary importance) as there is no evidence to suggest that their removal invariably cures HS. Hypothetically, identical HS lesions can therefore be produced by bacterial, immunological, chemical or physical factors affecting the predisposed hair follicle.

Pathophysiology

There is consensus that the pathophysiology of the disease involves hair follicle rupture and subsequent inflammation, sinus tract formation and scarring. Most likely, folliculitis is one of the most common pathological events in the human skin – and yet this leads to HS only in a minority of individuals. Why?

One possibility is the special biomechanical conditions in the affected follicles and concave skin regions. It has been suggested that the biomechanics of the predominant keratin found in the lesions is suboptimal, leading to repeated ruptures and development of lesions. The process may be further supported by the local biomechanical forces affecting the concave surface of, e.g. the axillae. It may be speculated that micro-tears of the hair follicle of predisposed individuals could be the primary event. Clinical observations support such a mechanism. If unspecified factors induce inflammation, the subsequent control of the inflammatory process may offer an alternative explanation. Either an excess of pro-inflammatory signals, or a lack of inflammation containing signals may lead to the development of HS. Indeed, studies have pointed to abnormalities in the immunity of HS patients (26,27).

Finally, the ‘containment’ or wound healing mechanisms of the host may play a role. The wound healing mecha-
nisms responsible for the scarring and sinus tract formation may depend on which cells from the damaged hair follicles are recruited. A group of stem cell-like cells have been identified in sinus tracts of HS lesions, and may provide the dynamic impetus for development of characteristic lesions (28). A better characterization of the specific wound healing-related characteristics of the hair follicles in individuals affected by HS may not only provide better insight into HS pathogenesis, but may also promote our understanding of the clinically challenging problem of fistula formation in general, not only in HS patients.

The scientific mind must be without prejudice, fertile and prepared to reject the ideas it has fostered. It will be interesting to see which of the ideas outlined here will survive.

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Viewpoint 2

I Fell Into A Burning Ring Of Fire
I Went Down, Down, Down
And The Flames Went Higher
And It Burns, Burns, Burns

The Ring Of Fire
June Carter Cash, 1962

After a cigarette is lit with a match, the match is perhaps thrown into the corner of the room. The glowing match is lying in the corner among dust, dirt, hair, microbes and grease. Slowly a fire starts. This tiny fire resembles the starting point of hidradenitis suppurativa (HS). The central question, then, is: What started the fire...?

Recently, it has been shown that that the primary event, the smallest fire of HS, is follicular retention by keratinized stratified squamous epithelium. HS would therefore appear to be a disorder of follicular rather than apocrine occlusion (1–6). Regardless of disease duration, follicular occlusion is an early and important feature in the pathogenesis of the disease. Three types of phenotypes on the basis of the expression of cytokeratins of the epithelial cells of the HS lesions have been suggested (7). Type I epithelium is cornifying, type II is non-cornifying, type III is non-cornifying and strongly inflamed. The three phenotypes are characterized as pathologically stratified squamous epithelium reflecting the dynamic process of inflammation, proliferation and stratification taking place in HS (7). Hyperkeratosis of the infundibular follicular epithelium occurs in response to androgenic stimulation.

As the fire of HS becomes a bit bigger, the plug becomes larger and then is invaded by bacteria from the skin commensal bacterial population, usually staphylococci. Hyperkeratosis of the follicular infundibulum forms comedo-like impactions which occlude the pilosebaceous apparatus. The keratinocyte-keratin complex is not easily broken down or resolved. This is followed by rupture of the follicular canal, and the extrusion of foreign material – e.g. corneocytes, bacteria, sebaceous matter and hairs – into the connective tissue induces the formation of an inflammatory infiltrate, which consists initially of granulocytes, followed by mononuclear cells and the formation of a foreign body-like granuloma. Epithelial strands develop and produce keratin. Squamous epithelium-lined sinuses, fistulas and secondary comedones are typical features (Fig. 1).

The leakage of the follicular content of bacteria and keratin into the perifollicular space causes more inflammation and an abscess develops. After emptying or absorption of the abscess contents the follicular epithelial cells line the lumen of the abscess and form sinusoids. These cells that line the sinuses and fistulae form masses of keratin harbouring a bacterial flora that lives in balance.
with the local immune system in this foreign body-like milieu. When the bacterial overgrowth in the epithelial keratin debris favours a vigorous chemotactic response with an inflammatory cellular infiltrate consisting of neutrophils, lymphocytes and histiocytes, abscess formation develops, the even bigger fire of HS, leading to the destruction of the pilosebaceous unit and eventually the other adnexal structures in the vicinity. Epithelial strands are generated possibly from ruptured follicular epithelium to form sinus tracts. If keratin-forming epithelial cells are left in the wound after surgery, the process can be set off again from this living cell remnant. This chronic inflammatory process causes severe deformation and fibrotic scar tissue (Fig. 1) with subsequent functional defects, representing the largest fire of HS.

Treatment of HS should aim to remove the causes of hyperkeratosis of the infundibular follicular epithelium. Thus, the follicular mass of the apoptotic keratinocyte–keratin complex can be eliminated, and bacterial overgrowth reduced, thereby inhibiting the formation of and promoting destruction of the epithelial strands in the abscess. Surgery is recommended early in the disease process and it has to be as radical as possible to minimize recurrence risk (8–22). The main features of the recently described carbon dioxide laser technique are in the blood-less surgical field, stepwise vaporization, radical removal of the inflamed tissues of HS, including its content of follicular epithelial cells all of which obviate local recurrences, with minimal destruction of healthy tissues (23–26).

Friction and small trauma might start the little fire, as well as the use of deodorants and depilatory products and shaving, which leads to minor primary lesions, boils, of HS that normally heal spontaneously in a week. Small balls of keratin are found in the openings of the boils. In the largest fire, i.e. when fistulas are formed, swelling of the keratinocytes occurs.

Overweight is unlikely to be causal but may be an exacerbating factor (27–31). Its importance in HS is probably due to shearing forces of skin and/or androgen effects. Weight loss may help control the disease. Keratin hydration is increased in sweat gland-rich regions of the body, and this has been shown to favour occlusion.

Genetics and endocrine factors may also contribute. Patients frequently report cases among their relatives (32–35). There appears to be an autosomal dominant inheritance with single gene transmission. One study supports the concept of a familial form of HS with autosomal dominant inheritance. A genome-wide scan was performed in a four-generation Chinese family to map the chromosome location of the responsible gene (36).

Finally, coming back to fire and cigarettes, smoking in patients with HS has been reported to be more frequent compared with that in controls (46–48). Smoking induces altered chemotaxis of polymorphic neutrophils which may play a role, similar to that in palmoplantar pustulosis. It seems reasonable that smoking cessation should therefore be strongly encouraged in patients with HS.

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Figure 1. Middle, right – a reddish brown ‘beefy’ ball, which is a Hidradenitis suppurativa sinus-surrounded inflammatory active connective tissue. The fat tissue close to the sinus has turned white due the inflammation.
References

Viewpoint 3
According to the ‘Dessau definition’ of hidradenitis suppurativa/acne inversa (HS), this is a chronic, inflammatory, recurrent, debilitating skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal and anogenital regions (First International Conference on Hidradenitis suppurativa, March 30–April 1, 2006, Dessau, Germany1).

Its prevalence ranges from one per 600 to four per 100 in the general population (1,2). HS affects more women than men, with a female-to-male predominance as high as 4:1. The majority of the patients are obese and smoke. The disease occurs almost always after puberty and before the age of 40 years. The apparent ‘rarity’ of HS in daily clinical practice may be explained by the prevalence of mild forms for which no consultation is sought, the weariness of HS patients discouraged by previous treatment results to seek further medical help, and by the generally poor level of education in the medical community on the proper recognition and management of HS (this is manifest from the often very late time at which the correct diagnosis is made, in the long run). The latter is particularly regrettable, as the psychological impact on affected patients can be very substantial, encompassing major social, personal and occupation challenges. Together with the sequelae of the disease, including dermal contraction, keloid formation, restricted limb mobility, lymphoedema and fistula formation, this dominates the long-term burden of disease and greatly diminishes a patient’s quality of life.

Aetiology and pathogenesis of HS are still unknown. Current theories implicate hyperkeratosis of the follicular epithelium as the morphological hallmark of HS pathogenesis, leading to occlusion of the apocrine glands with subsequent follicular rupture, inflammation and possible secondary infection (3,4). From the genetic point of view, the group of experts who participated at the First International Symposium has accepted that HS must be a polygenic disease, with sporadic cases having defects in a number of critical genes involved in its pathogenesis and familial cases with a probably highly penetrant defect(s) in one of these genes.5

Hidradenitis suppurativa has given rise to a number of lively clinical debates, such as the discussion on the exact skin appendage involved (eccrine sweat glands, apocrine glands or terminal hair follicles) and the discussion on the pathogenetic background, namely a genetic, hormonal, bacterial, genuine inflammatory, environmental or physical one. The significance of gender, body mass and smoking on disease prevalence is still under investigation. The major therapeutic challenge in HS is the optimal choice between antibiotics, retinoids, corticosteroids, incision and drainage, local wound care, limited versus radical local excision, radiation, laser therapy and modern drugs, such as biologics, all

of which have been proposed – and whose relative importance and usefulness have been controversially debated.

**Which is the exact skin appendage involved?**

One of the major debates in HS is the determination of the exact skin appendage involved. Although initially accused, the apocrine gland is probably ‘innocent’: neither exist significant differences in the size and density of the apocrine glands in HS patients compared with normal controls (5), nor significant morphological abnormalities of the apocrine glands in diseased skin areas (6,7). No primary apocrine involvement is detected; and the one-third of HS cases that present inflammatory changes involving the apocrine glands represents cases of very extensive inflammation that also engulf other structures such as the eccrine glands and hair follicles.

A consistent finding in histological studies of HS is a follicular occlusion regardless of disease duration (8). The majority of specimens (50–85%) contain poral occlusion, sinus tracts or cysts (7). The histopathology of HS supports its classification to the follicular diseases. Newly formed nodules show an occluding spongiform infundibulofolliculitis with secondary involvement of apocrine glands (9), i.e. a disease of the follicular epithelium in the terminal hair follicle.

Different from acne vulgaris, HS is localized in non-facial regions, where there are terminal, pigmented, coarse hairs, as in the axillae, groins, anal fold, mons pubis and scalp. These regions affected by acne inversa tend to be rich in apocrine glands, which are part of the apocrine-pilosebaceous unit and can be engulfed in the inflammatory process. The sebum excretion rate is not increased in HS.

The earliest inflammatory event in acne inversa is a segmental rupture of the follicular epithelium, followed by spilling of foreign body material, such as corneocytes, bacteria, sebum products and hairs, into the dermis. The dumping of foreign products initiates an inflammatory response provoking foreign body granuloma, and epithelial strands try to encapsulate the necrotic tissue. Once rupture of the follicular epithelium has occurred, the disease spreads rapidly. The draining sinus is a late complication of HS.

**Hidradenitis suppurativa and genetic predisposition**

Genetic factors may contribute to HS susceptibility. Patients frequently report HS cases among their relatives. In one study, 18 of 70 patients with HS (26%) had a positive family history, whereas in 96 control subjects matched for age and sex, who did not have HS, only two of their relatives suffered from HS (10). There appears to be autosomal dominant inheritance with single gene transmission (10,11). A variable degree of gene penetrance and possibly hormonal influence on gene expression may explain the reduced risk to first-degree relatives, which falls short of the expected 50% found in the study.

**Hidradenitis suppurativa and autoimmunity**

Clinical improvement with the application of therapies targeted against tumour necrosis factor (TNF-α) may be compatible with the above theory of pathogenesis, as TNF-α is a major proinflammatory cytokine. In these studies, monoclonal anti-TNF-α etanercept receptors (12,13) or soluble TNF-α infliximab antibodies (14) were administered in a small number of patients. Positive responses with anti-TNF-α therapies have also addressed the question of whether any probable autoimmune predilection might contribute to the pathogenesis of HS (12). Based on the above probability for the existence of some derangement of the activity of the host immune function, a current study has shown a reduction in the percentage of natural killer cells over time and a lower monocyte response to triggering by bacterial components in patients with HS (15).

**The role of hormones in hidradenitis suppurativa pathogenesis**

The occurrence of HS in a narrow age spectrum and in obese individuals as well as the female predominance have led to the theory that a hormonal component may be involved in the pathogenesis of HS (16). Flare-ups have been linked with menses (17); shorter menstrual cycles and longer duration of menstrual flow are associated with the disease (18). Onset after menopause is rare (19). Sex hormones may influence HS; association with acne vulgaris, comedones and hirsutism, development post puberty, general decline in disease activity seen at the climacteric, and improvement seen during pregnancy have been reported (20–22). On the other hand, although most HS patients have normal androgen profiles (23), there have been reports of symptomatic improvement with the use of anti-androgen therapy (23–25). Indeed, HS has been regarded as an androgen-dependent disorder (26). HS is rarely a presenting feature of premature adrenarche, leading support to the view that it is androgen-dependent (27).

It has been suggested that enhanced peripheral conversion of androgens by apocrine glands plays a critical part in its pathogenesis (26). However, equivalent activity of three peripheral androgen-converting enzymes in axillary apocrine glands of subjects with HS was similar with those of controls (28). A relationship between HS and hyperandrogenism is largely based on the finding of an increased free androgen index (testosterone/sex hormone binding globulin, SHBG) due to a low SHBG, but the subjects were not controlled for body mass index (BMI) (20). This finding is compromised, as many subjects are significantly overweight (21) and SHBG is negatively correlated with BMI (29). Another study could only demonstrate...
hyperandrogenism in a subgroup of women who did not experience a premenstrual flare in their disease (21) but no supporting evidence for hyperandrogenism or suppression of SHBG has been found in women with HS compared with age-, weight- and hirsutism-matched controls (19).

Hidradenitis suppurativa has also been reported to be associated with classical endocrine disorders, such as Cushing’s syndrome (30) and acromegaly (31). This may be interpreted as further indication that hormonal factors may play a significant role in HS pathobiology.

Outlook
In the era of molecular genetics, new diagnostic possibilities are emerging: gene expression profiling can be applied to compare the gene expression pattern in the apocrine gland-bearing areas of the body of HS patients versus healthy individuals. Bioinformatics will help to identify the most relevant among the differentially expressed genes. This may provide valuable insights into the basic pathologic processes occurring in HS and may identify genes and biochemical pathways that could act as new targets for classical drugs in the treatment of HS.

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Viewpoint 4
Greek methodology has created the term ‘labyrinth’ for the convoluted indoor maze (Fig. 1a) that, according to legend, was constructed for King Minos of Crete (after the design by Daedalus) to hold the Minotaur (1), a creature half-man, half-bull.

Ranging from its clinical and histological presentation to the many open questions posed by its pathobiology, hidradenitis suppurativa (HS), in many respects, represents such a labyrinth. Clinically (Fig. 1b), and on histological analysis (Fig. 1c), the undermined sinus tracts in HS indeed resemble a labyrinth (2). Despite intensive studies of HS (3), the aetiology of HS still remains unclear, and we are still trapped in a maze of possibilities and conflicting hypotheses.

Let us walk, then, through this labyrinth, searching for the Minotaur around which it may have been built.

This is best performed by considering selected key questions in HS research. The most pressing ones arise immediately, if one more carefully contemplates on: (a) the clinical signs and symptoms presented by HS patients; and (b) the proposal by Plewig et al. (4) that the term ‘HS’ should be changed to ‘acne inversa’.

What are the differences in clinical manifestation between HS and acne vulgaris?
The characteristic lesions in HS are deep-seated subcutaneous nodules or abscess (2,5). In acne vulgaris, the primary lesions are either open or closed comedones (2,6). In HS, closed comedones are never present, and open comedones can be found as secondary lesions, but they are absent in early lesions of HS (2). They may appear in long-standing HS. Thus, the clinical appearance of HS and acne vulgaris is quite distinct, and it adds little to our understanding of HS pathogenesis to adopt the ‘acne inversa’ terminology.
Are terminal hair follicles really the main theatre of HS action?

Plewig and Kligman stated that HS occurs in the terminal follicle bearing pilosebaceous unit (2,4). If this were so, we should find multiple thick hair shafts in HS. However, this is not really the case, and at least clinically (as opposed to histologically) terminal hair follicles actually are not the primary target in HS. In fact, despite some overlap, the areas of predilection for HS and the skin regions richest in terminal hair follicles seem to be rather distinct territories. In men, the buttock, a commonly affected site of HS lesions, bears hardly any terminal hair follicles at all. In addition, if terminal hair follicles were the key targets of HS, multiple tufted terminal hair shafts from the follicle should be observed in HS, as is characteristically seen in folliculitis decalvans (Fig. 2), dissecting folliculitis and peri-folliculitis abscedens and suffodiens (Hoffman). Instead, multiple thick long terminal hairs are features one fails to notice in the characteristic fistulae of HS (Fig. 3).

Thus, from a clinical perspective, it is quite dubious whether HS really occurs, as frequently claimed and reverberated uncritically, in terminal (rather than in vellus) hair follicles.

But what about the apparent histopathological evidence for a predilection of HS for terminal hair follicles? Plewig and Kligman describe three types of hair follicles: vellus hair follicle, sebaceous follicle and terminal hair follicle (2). Well, in my personal experience, it is very difficult (if at all possible) to histologically detect terminal hair follicles in HS. Even in standard textbooks (2,4,7), the classical characteristics of terminal hair follicles (thick, medullated hair shafts and large sebaceous gland), as described so beautifully in Plewig’s book (2), are essentially absent in HS. Instead, Layton et al. (7) have observed tiny vellus hairs in follicular canals in HS. The lower part of hair follicles and sebaceous gland are uninvolved in HS. Taken together,
Figure 4. CK 14 is expressed in the protruding epithelium in a leaf-like structure.

going hypothesis.

The sinus epithelium in HS is not a late, but a very early event and does not primarily arise from the hair follicle epithelium, but by invagination from the epidermis (Fig. 1c). This invagination of the epidermis may result in the formation of infundibulum-like epithelium that protrudes into the deep dermis as epidermal cysts. Resident microflora may cause the adherence of the epithelium.

Therefore, it is very dubious that HS predominantly affects terminal hair follicles.

Thus, even from the perspective of histopathology, HS is not a disorder of the terminal hair follicle. The fundamental change in HS is the retention hyperkeratosis of the infundibulum (2,4,7,8). More likely, HS predominantly occurs in the infundibulum of vellus hair follicles, whose tiny shafts can be observed in the follicular canal of affected pilosebaceous units.

The keratin expression pattern in HS has been studied immunohistologically (9,10). Among cytokeratins, CK17 is neither expressed in the cyst wall in most cases of HS (9) nor is found in the pilonidal sinus of HS (11). CK 14 is more pronounced in the protruding epithelium in HS (9) (Fig. 4) In terminal hair follicles, CK 16 is detectable in the lower portion of hair follicle below the opening of sebaceous duct (9–12). The fact that CK16 was only found in two of 16 HS cases (9); therefore, further argues against terminal hair follicles as key targets in HS pathogenesis. However, as these immunohistological results illustrate, HS is definitely associated with abnormalities in keratinization. The next questions, then, are as follows.

What causes retention hyperkeratosis, and how does this lead to the characteristic, labyrinthic sinus tracts of HS?

Based on the above keratin expression patterns and the unconvincing evidence that terminal hair follicles are the key organ where HS manifests itself, I propose the following hypothesis.

The sinus epithelium in HS is not a late, but a very early event and does not primarily arise from the hair follicle epithelium, but by invagination from the epidermis (Fig. 1c). This invagination of the epidermis may result in the formation of infundibulum-like epithelium that protrudes into the deep dermis as epidermal cysts. Resident microflora may cause the adherence of the epithelium.

Coagulate-negative Staphylococcus (CNS), in normal flora on the skin, is the most common bacterium isolated from HS lesions (13). CNS is also the most common bacterium isolated from epidermal cysts (14). Therefore, CNS may tend to adhere to the adjacent, closed serrated epidermis in the intertriginous area, resulting in infundibular-like epithelium (cyst formation) in both HS and epidermal cyst. An alternative explanation may be that HS patients exhibit an altered immunologic response to CNS antigens, compared with normal individuals. Another possibility is that anaerobic bacteria (15) play a key role in retention hyperkeratosis, resulting in both sinus and cyst formation.

Often, the protruding epithelium that forms from the wall of HS cysts shows a leaf-like structure, as shown in Fig. 4. Why do such leaf-like structures arise? Formation of the epithelial and mesenchymal interactions might be related to undifferentiated keratin expression (CK14). In addition, anastomosing epithelium that links sinus tracts into a complex maze of tracts is frequently found in HS (Fig. 1c). Kurzen et al. (10) studied desmoplakin and desmocollin in epithelia in HS, and demonstrated their differences between three types of epithelium (10). Altered epithelial adhesion properties in HS might also result from abnormalities in e-cadherin expression.

Is the clinical phenotype of HS determined by an abnormal immune response against bacteria?

It is clear that bacterial infection is not the primary cause of HS. However, bacteria, their products, and immune responses raised against bacterial antigens may well greatly influence the clinical phenotype of HS lesions as well as the course of HS in any given patient. From normal skin microflora, CNS, Staphylococcus aureus, Streptococcus, Peptostreptococcus, etc. are isolated in HS, e.g. in perirectal and vulvovaginal lesions (16,17). However, it is unclear whether these clinical isolates are involved in the pathogenesis of HS or not. CNS obstructs the intra-epidermal sweat duct, resulting in miliaria formation (18). Thus, it is conceivable that sinus formation in HS involves a similar mechanism.

In terms of natural immunity, patients with HS may respond abnormally to these bacteria (e.g. Propionibacterium acnes), whose products stimulate Toll-like receptors (19), producing pro-inflammatory cytokines such as IL-1α, and giving rise to abnormal keratinization (20). The hair follicle was recently recognized as one of the immune organs of skin (21). In particular, the infundibulum, which belongs to the distal arm of the human hair follicle immune system, appears to represent a special organ involved in immune response (22). These areas are the preferred sites for perifollicular inflammatory cells in dermatoses such as lichen planopilaris, systemic lupus erythematosus, scleroderma and folliculitis decalvans (23).
Therefore, HS may just represent a certain clinical phenotype that reflects a disturbed hair follicle immune system.

Important studies that remain to be performed in HS research
In consequence, infundibular immunology, therefore, needs to be systematically dissected in future. For example, Toll-like receptors may be related to the initiation of inflammation in the infundibulum. In this context, the impact of pro-inflammatory cytokines on abnormal keratinization in HS should also be carefully investigated.

Other important areas for future HS research include for example the precise mechanism by which new epithelium is formed in the process of sinus drainage (in HS and other diseases where this occurs). Scar formation involves a cell-mediated response that deserves study to clarify the pathogenesis of HS, like in acne vulgaris (24). With regard to possibly increased carcinogenesis in HS, the CK expression in well-differentiated SCC arisen from HS epithelium is similar to that in normal infundibulum (25). By contrast, poorly differentiated SCC in HS contained simple epithelial keratins (CK7, 8, 18, 19). Thus, it deserves to be carefully studied whether CK expression patterns reflect the clinical prognosis. Finally, the terminal stage of keratinization is related to filament-aggregating protein (filaggrin), a major component of keratohyaline granules (26). Filaggrin expression has been linked to the pathogenesis of acne vulgaris (27), epidermal cyst (28) and nevus comedonicus (29). Therefore, an immunohistochemical study of filaggrin expression should be undertaken. As comprehensive ultrastructural studies of HS remain to be performed, this should be complemented by electron microscopy.

In the long run, at least the ‘floor plan’ of the HS labyrinth is becoming better defined, defined scenarios can be developed on how it is being constructed and evidence is emerging that its epithelial walls show distinct abnormalities of keratinization.

But what is the Minotaur it may contain?

Viewpoint 5
Before you read these comments, the authors want you to know that we have a ‘conflict of interest’ – we do not believe in ‘hidradenitis suppurativa’! While we will not be engaging in a terminological debate, in our opinion ‘acne inversa’ is the appropriate term for this often devastating disease (1). It is a term which – in a nutshell – already puts forth part of our answer to the introductory question posed by the editor: What causes hidradenitis suppurativa?

‘Acne inversa’ indicates that this is a disease of follicular occlusion similar to acne vulgaris. Pathogenetically, however, more can be said about what does not cause ‘hidradenitis suppurativa’ than what causes it.

Similar to other forms of acne, apocrine glands have no role in acne inversa; the glands are guilty by association only and as such are merely ‘innocent bystanders’ (Fig. 1). This is documented in numerous studies (1–6). The early experimental model for ‘hidradenitis suppurativa’, published in 1955 by Shelley and Cahn (7), was designed to...
recapitulate the changes seen in patients with ‘hidradenitis suppurativa’ and relied on the application of belladonna adhesive tape to manually depilated axillary skin. It was one of the most important papers emphasizing the central role of apocrine glands in the disease process but was plagued with flaws and assumptions, although the conclusions derived from it were considered dogma – at least for many years. In our opinion, the paper did not deserve the attention it got and the attention was uncritical.

Knowing that at centre stage in ‘hidradenitis suppurativa’ is follicular occlusion, the question remains what causes it or – more specifically – what causes it in the axillae and in the groin area, the predominant anatomical locations (hence the term acne *inversa*). It is well documented that obese females are most commonly affected (8–11). Normal axillary skin displays already a ruffled appearance under the microscope (Fig. 1a) as opposed to the even epidermal surface observable in biopsies, e.g. from facial skin. We speculate that constant friction in the axillae and in the groin, enhanced by obesity, is the major biomechanical factor contributing to microcomedo formation from which the subsequent cascade of pathogenetic events initiates. Microcomedones are part of the histopathological spectrum of early disease (1,12). Especially the folds observable in the skin of obese individuals contribute mechanically to the retention of corneocytes, hair shafts and sebaceous secretory products within the microcomedones, leading to their enlargement and later rupture. The hair follicles in ‘hidradenitis suppurativa’ exhibit an abnormal shape, are wider in the deep dermis and are also larger in the axilla (13). We interpret this finding as corroborating our biomechanical theory.

A close relative of ‘hidradenitis suppurativa’ and part of the acne tetrad (14), the pilonidal sinus, is equally caused in our opinion by biomechanical factors. Known also as ‘jeep disease’ (15), it has a predilection for soldiers subjected to long-term occlusive sitting conditions (16,17).

Outside the intertriginous areas, the human body employs clever mechanisms to combat mechanical retention. A good example is the external auditory canal, where a peculiar pattern of keratinocyte migration occurs for the sole purpose of keeping the meatus free from desquamation products (18). The epidermal front of the mucocutaneous junction of the tympanic membrane simply expresses hyperproliferation-associated cytokeratins and such keratinocytes migrate, thus preventing their accumulation and allowing also cerumen to be disposed to the outside.

Epidemiologically, it is known that most patients with ‘hidradenitis suppurativa’ are smokers (19–21). A recent intriguing paper by Hana et al. (22), one of the few experimental studies in the field, convincingly demonstrated the induction of infundibular epithelial hyperplasia by nicotine...
as a prerequisite for follicular plugging. The authors employed organotypic cultures and suggested the non-neuronal acetylcholine receptors, prominent around the follicular infundibulum, as the nicotine-mediating effector system (22). This would be the first logical explanation of why mostly smokers are predominantly affected by the disease and also confirms our findings of microcomedones as an early pathogenetic event. While we do not think that nicotine is the inducing factor, it certainly is a major contributing factor of 'hidradenitis suppurativa'. In later disease stages, nicotine seems to be less important, as the non-neuronal cholinergic system is not prominent in sinus tracts (22). By then, however, the disease has already developed a life of its own. Nicotine is also secreted in apocrine and eccrine sweat (23), which may play a direct role in 'hidradenitis suppurativa'. It remains speculative if, in addition to nicotine, tar products in cigarette smoke are secreted via sweat and find their way to the follicular infundibula, thereby exerting their well-documented comedogenic effects.

From the above, it is obvious that we are in dire need of more basic science data on this enigmatic disease, foremost to help our patients. They may otherwise fall into the trap of alternative or holistic medicine using the lack of knowledge about 'hidradenitis suppurativa' to its commercial advantage by selling products with no therapeutic benefits, such as algae (http://www.akne-inversa.de/projekt/spiru-studie/index.htm), thereby extending the ordeal of the patients and preventing them to seek adequate treatment.

Reflecting on 'What causes hidradenitis suppurativa?' we are still astounded that even the current fragmented level of knowledge on 'hidradenitis suppurativa' cannot be comprehended by many representatives of allopathic medicine. An especially baffling example is that of a well-known cosmetic dermatologist from Nashville, TN, who asked for copyright permission for histological photographs from our own paper on acne inversa (1). After reproduction of the photomicrographs, he elaborates in his review on the application of photodynamic therapy for 'hidradenitis suppurativa': 'Because HS [= hidradenitis suppurativa] is an apocrine disorder, and not a sebaceous gland problem [...] (24). This is the exact opposite of what we have hoped to rectify with our histological pictures. We hope the reader of this commentary is not a cosmetic dermatologist!

Commentary 1

Hidradenitis suppurativa (HS) is a devastating chronic skin disorder affecting areas rich in apocrine glands. HS is in most cases recalcitrant to therapy (1). Therapy decision making largely depends on the impression of the physician about pathogenesis of HS. This may be connected to the high rate of treatment failure (2). HS was initially conceived as an infectious disease process or as a form of acne. Patients run a life of exacerbations and remissions with

References

heavy purulent discharge from the affected areas. The presence of pus creates the impression of an infectious disease which is compatible with the traditional theory of pathogenesis. In that theory, follicular hyperkeratosis leads to occlusion of the apocrine glands with secondary infection from bacterial skin flora (3). As a consequence, antibiotics are prescribed. Even though antibiotics may offer relief of symptoms, cessation of treatment is usually accompanied by flare-ups (4). This creates serious doubts if HS is indeed an infectious process or not. The fate of treatment with retinoids is similar (5).

Surgical excision of the affected areas is accompanied by high recurrence rates (6,7). Carbon dioxide laser locally applied for the management of 35 patients with Hurley II lesions ended in recurrence in 25 patients. Surprisingly, relapse supervened in another anatomical region, different from the one which was operated (8). Re-appearance in another site after immune triggering is a characteristic of auto-immune disorders which creates the hypothesis if HS is an autoimmune disorder. This is compatible with the coexistence of HS with other auto-inflammatory disorders like Crohn’s disease (1).

In a recent study of our group (8), peripheral blood monocytes were isolated from 53 patients with active HS and stimulated with bacterial endotoxin (LPS) for the production of pro-inflammatory cytokines, namely tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Cells isolated from six healthy volunteers were controls. It was found that monocytes of patients with HS were weaker producers of cytokines compared with healthy controls. In the same study, it was shown that percentages of natural killer (NK) cells were decreased in parallel with the natural history of HS (Fig. 1). These findings favour the existence of significant alterations of innate immune functions of HS patients. They also support indirectly an auto-immune aetiology as antigen presentation is based on the integrity of the innate immune system.

The concept of HS as an autoimmune disorder is also based on the favourable responses of patients to targeted therapies against TNF-α. Infliximab, a chimeric anti-TNF-α monoclonal antibody, and etanercept, a soluble receptor of TNF-α, have been administered in case-studies with limited number of patients and at a variety of dose regimens. Results of infliximab were contradictory in terms of safety and efficacy in case-studies of five and seven patients each (9,10), whereas etanercept was effective and well tolerated in a series of six patients (11).

The only open-label prospective study on the safety and efficacy of a specific regimen of etanercept has been published by our group (12) (EudraCT: 2004-004555-19, http://www.clinicaltrials.gov, NCT00329823).

Etanercept was administered at a dose of 50 mg once weekly for 12 weeks in 10 patients. A more than 50% decrease in the Sartorius score was found in six patients at week 12 and in seven patients at week 24. A considerable decrease in the total number of fistulas from the baseline was seen over all weeks of follow-up. Eight patients reported recurrence of drainage of pus from the affected areas within 4–8 weeks after the end of administration of etanercept.

There is accumulating indirect evidence for a key role of the immune system in HS pathogenesis. Derangements of the innate immunity, favourable responses to therapy with etanercept and exacerbations upon cessation of anti-TNF-α treatment, support auto-immunity as the underlying cause of HS.

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Commentary 2

Although recognized more than 150 years ago, hidradenitis suppurativa (HS) is still a mysterious disease. Ever since inflammation of the apocrine glands was recognized as a secondary event in the pathogenesis of the disease, it has been speculated that comedonal and/or poral occlusion(s) and bacterial infection play a crucial role. Even though this concept has been questioned almost immediately, there is some consensus regarding the role of immunity and infection. Thus, even if I cannot provide an answer to the question posed by the editor, let me elaborate on the issues of skin immune response and infection in HS pathogenesis.

The involvement of immune response in HS remains controversial. Immunological investigations of patients with HS suggested no abnormalities of the immune system (1). By contrast, other authors showed increased peripheral suppressor T-cell activity (2), indicative of a cellular immune response. This is further supported by the presence of activated, HLA-DR-positive as well as Leu-8-positive immunoregulatory lymphocytes (3). These results indicate that the lymphocytic infiltrate is definitely the result of in vivo activation of lymphoid cells. Indeed, the significant fall of the T-helper/suppressor and NK cell ratio over time after the initiation supports the existence of a precipitating, cell-mediated immune response with only a short eliciting period (3,4). More recent studies have shown that dysfunctional neutrophils and monocytes may also be involved in the pathogenesis of HS, still, no primary abnormalities of the innate or acquired immune system can be held to be causal in every case (3–6).

Because of increasing evidence suggesting that keratinocytes (KC) not only participate in cutaneous immune response but may in fact play key initiation roles (7), one must also consider the contribution of KCs to HS pathogenesis. KCs are able to recognize a wide variety of micro-organisms through their pattern recognition receptors (PRRs) and have evolved mechanisms to distinguish between skin commensals and pathogens. Signalling through specific PRR combinations provides selectivity and specificity of immune response. As a result, KCs produce a wide range of antimicrobial peptides, proinflammatory cytokines/chemokines and inducible enzymes (8). The secretion of antimicrobial peptides is indeed crucial, as skin lesions characterized by low levels of such host-defence peptides are more susceptible to infections. By exhibiting chemoattractant activity, KC-derived cytokines/chemokines and antimicrobial peptides can recruit T cells, neutrophils and dendritic cells into sites of infection, thus providing an improved immune response against pathogens (7,8). These findings indicate a close interdependence of KCs and inflammatory infiltrate as well as a balance between the innate and acquired immune systems. Any perturbation in this system, for example dysregulation and abnormal expression of inflammatory mediators or their receptors in KCs, can lead to the pathogenesis of chronic inflammatory skin diseases, such as HS.

The significance of bacterial involvement in the pathogenesis of HS is also controversial. It is likely that chronic inflammation is because of secondary bacterial colonization (5). This is further supported by the fact that routine cultures from the surface of the lesions are often negative. Still, bacteria are likely to be involved in the pathogenesis of the disease as numerous species are most frequently isolated from lesions (6,9). Most of bacteria identified in HS lesions, such as Propionibacterium acnes and coagulase-negative staphylococci, are part of the normal microflora, but have also gained attention as pathogens. These findings highlight a possible polymicrobial nature and predominance of anaerobic bacteria, supporting the role of bacterial infections as a possible pathogenic event in HS. However, interpreting the results of previous studies is difficult, as potential differences amongst recently discovered phylogenetic groups and/or ecotypes have not been taken into account. Notably, the existence of phylogenetically distinct P. acnes clusters have recently been demonstrated (10). Importantly, these clusters differ in the production of secreted proteins (11), and induce different immune responses in KCs and sebocytes (12,13).

These findings challenge our current understanding of the pathogenic nature of bacteria involved in HS pathogenesis and raise the exciting possibility that bacterial strains, or group of strains, with greater potential to cause opportunistic infection in HS may exist. This may explain, in part, the apparent controversy with respect to the role of bacterial infection in HS.

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Commentary 3

Hidradenitis suppurativa (HS) has originally been considered a disorder of the apocrine glands. However, over the years more and more authors suggested HS to be a misnomer as the disease seems to start rather with follicular occlusion than with a primary involvement of apocrine sweat glands. Since 1989, the term acne inversa (AI) is commonly used instead of HS to underline that this disorder is actually a defect of follicular epithelium. This concept does, however, not explain sufficiently the causes of follicle involvement and possible subsequent follicle rupture.

When discussing with colleagues of different medical disciplines, we often are under the impression that the experts treating this disease have split in two camps – rigorous supporters of the term HS, and equally stern supporters of the term AI. The ongoing conflict between these two hostile camps may actually have put basic HS research into a kind of ‘hibernation’, rather than having promoted scientific breakthroughs in this obscure, but very important chronic inflammatory disease.

As a provocative approach to possible causes of HS or AI is favoured on these pages, we therefore would like to modify the question raised by the editor into one that often rises in clinical routine: Do all patients that we treat for HS/AI really suffer from the same disease?

From the point of view of daily clinical routine, we have long wondered about the extremely different patient populations that are referred to our clinic with a diagnosis of HS or AI. Some of our patients report acne vulgaris to have occurred in their medical history. Theses patients often show clinical signs or remnants of a previous severe acne, most often presenting as typical scarring of the face and back. Others still have active acne lesions. These patients often do not show obesity (which has been claimed to be a characteristic of HS patients). Instead, they usually present comedones within or surrounding the inflammatory lesions. Interestingly, in our experience, these patients frequently respond to retinoid treatment, whereas the majority of HS patients do not benefit from retinoid.

By contrast, there are the classical obese smoking HS/AI patients with chronic inflammatory lesions, which support the concept that nicotine and obesity present a significant risk factor. Compared with the normal-weight patients, we rarely notice any comedones in this patient population at all, even in early lesions or healthy surrounding skin.

A third type of patient, although less frequently encountered, presents with typical HS/AI lesions in conjunction with granulomatous colitis (Crohn’s disease). We have never seen comedones in this collective. Are these patients really suffering from the same type of HS or AI as is present in slim patients with a prominent history of acne vulgaris, or the obese smoking female patients?

Based on clinical observation and experience, we hypothesize that we do not deal with the same pathobiological entity in all patients that meet currently accepted diagnostic criteria for HS or AI. Further studies with an accurate and refined definition of distinct patient subcollections is likely to also provide new answers to the central question that drives these CONTROVERSIES.

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Viewpoint 6

Hidradenitis suppurativa (HS) is a chronic inflammatory, disabling disease that has been shown to emerge from the pilosebaceous unit of the intertriginous areas and is hence preferentially called acne inversa in the European literature. HS is certainly a multifactorial disease based on a genetic background with different triggering factors. The genetic background that predisposes the individual for HS has so far escaped elucidation. First attempts to localize the HS susceptibility locus to chromosome 1q have not been confirmed by other groups (U. Radhakrishna, Omaha, USA). By contrast, different triggering factors are well known, amongst which tobacco smoking, sweating, obesity and colonization with Staphylococcus aureus seem to be the most important.

In the following, I would like to place full emphasis on what I consider a still insufficiently appreciated aspect of HS, i.e. why and how tobacco-smoking is involved in HS pathogenesis:

1 Between 80–90% of HS patients are active smokers, which designates HS, together with, e.g. pustular palmoplantar psoriasis, a clearly tobacco-related skin disease (3, 4). In a questionnaire-based study, we have noticed that HS...
patients develop new lesions after surgical therapy only if they continued smoking (4).

2 Nicotine is the main toxin in cigarette smoke and reaches serum levels of 50–500 nM (5), while in axillary sweat nicotine concentrations of up to 150 nM have been measured (6). After smoking one cigarette, nicotine can be detected for up to 7 days in axillary sweat, indicating a slow metabolization rate (7). Thus, due to the density of sweat glands and the occlusive milieu in the intertriginous areas, nicotine is present on the surface in relevant pharmacological concentrations, higher than elsewhere on the skin. This observation would explain the distribution of HS lesions and the interdependency to sweating, provided nicotine really is a major pathogenic factor in HS.

3 As a natural alkaloid occurring in plants, nicotine has a selective antimicrobial activity. An important exception in this is S. aureus, the growth of which is actually favoured by nicotine (8). Consequently, HS patients are, like smokers in general, heavily colonized with S. aureus (4,9). This vicious circle is closed by the fact that S. aureus has been shown to stimulate the expression of choline-acetyltransferase (ChAT), the rate-limiting enzyme in the synthesis of acetylcholine (ACh) (10). ACh, in turn, can stimulate S. aureus growth – analogous to nicotine (Fig. 1a,b).

4 Indeed, the production of ACh in human skin (as suggested by ChAT immunoreactivity) is limited to keratinocytes, sebocytes, endothelial cells, lymphocytes and neutrophilic granulocytes, finding its peak in peri-infundibular basal keratinocytes of HS patients (blue line in Fig. 1a,b) (11).

5 The natural ligands of nicotine are nicotinic acetylcholine receptors (AChR) that can be found in a highly complex composition on all cells putatively participating in the pathogenesis of HS: keratinocytes, sebocytes, mast cells, neutrophilic granulocytes, lymphocytes and macrophages (12).

6 Despite their somewhat misleading name, not all nAChR are stimulated by nicotine. While nicotine leads to calcium influx in homopentameric α7 nAChR and to sodium and/or potassium flux after binding α3* nAChR

Figure 1. Proposed sequence of events in the pathogenesis of acne inversa: Nicotine fuels the vicious circle of ACh production and Staphylococcus aureus growth (a) promoting chemotaxis of neutrophilic granulocytes and degranulation of mast cells (b). In addition the infundibular epidermis becomes increasingly hyperplastic leading to follicular obstruction (b). Influx of neutrophilic granulocytes and mast cell degranulation promote a spongiotic infundibulitis. The acute phase is followed by a chronic phase characterized by the appearance of lymphocytes and macrophages (c) culminating in the rupture of the hair follicle (d). Draining sinus are formed in an attempt to eliminate residual hair-shafts. ACh Acetylcholine, ASG apocrine sweat gland, ChAT choline acetyl transferase, ESG eccrine sweat gland, GC foreign body giant cell, HF hair follicle, LC lymphocyte, MC mast cell, NG neutrophilic granulocyte, Mph macrophage.
(13), in both α9 and α10 nAChR, ion flux is actually inhibited after nicotine exposure. Therefore, in the presence of, e.g. both α7 and α10 nAChR the dominating effect is hard to predict and may be determined by AChR subunit density (remains to be determined) (12).

Nicotine has been shown to promote inflammatory reactions, especially in the presence of mast cells and neutrophilic granulocytes, both of which have been shown to be present in early lesions of HS, causing a spongiotic infundibulitis (1). Specifically, nicotine provokes mast cell degranulation (14) and enhances chemotaxis and survival of neutrophilic granulocytes (15,16).

To terminate an inflammatory reaction induced by micro-organisms, cell debris or by ‘foreign’ material (hair keratin!) in the chronic phase of HS lesions, both lymphocytes and macrophages secrete and need proinflammatory cytokines like TNF-α, IL-4, IL-2 or IL6 (Fig. 1c,d). Nicotine has been shown to suppress the LPS-induced secretion of these cytokines (10,17). In addition, chemotaxis of macrophages is diminished in the presence of cigarette smoke extract, an effect attributed to nicotine (18).

Nicotine is a highly potent inducer of epidermal hyperplasia as we could show in an in vitro model. This corresponds to the prominent, approximately threefold increase in epidermal thickness observed in HS specimens (compare Fig. 1a–d). At the same time, the density of nAChR is most pronounced at the place where HS pathogenesis is thought to originate from: the hair follicle infundibulum (11).

Altogether, there is overwhelming evidence for a crucial role of nicotine and the non-neuronal cholinergic system in the pathogenesis of HS, providing a molecular mechanism especially for early events in HS pathogenesis, which is follicular obstruction and infundibulitis. Late events are more complex, but even those may still be prominently be influenced by nicotine, e.g. by impairment of macrophage and lymphocyte functions.

Clearly, further studies are needed to verify the presented novel hypothesis of HS as a disorder of over-stimulation of defined nicotinergic AChR, and to test the new therapeutic strategy that is invited by this HS pathogenesis scenario: the systematic use of anticholinergic agents in the management of HS.

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