What causes acne inversa (or hidradenitis suppurativa)? – The debate continues

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The Journal Reviews published was incomplete. The Journal Reviews should have read as follow:

What is the utility of critical evaluation of our lexicon? As our understanding of pathogenesis evolves, we become better able to reappraise and reclassify diseases. One may argue that as long as we understand the disease process, there is no harm in allowing misnomers to continue. However, misnomers convey a false impression of pathophysiology, thus hampering our ability to communicate effectively with colleagues in other specialties. As our understanding of medicine and the interconnection of diseases deepen, clarity of communication is imperative. The following discussion reviews several

publications on hidradenitis suppurativa, one of which is an in-depth discussion of the pathogenesis. Knowing the pathogenesis also allows for a proper nomenclature.

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'Hidradenitis suppurativa' is a devastating disease. The term conveys that the primary pathogenic event is centered on the (apocrine) sweat glands, a concept dating back to the original description of the disease by Verneuil[1] in 1854 (quoted by Sellheyer and Krahl[1]) and supported by an early experimental study by Shelley and Cahn[2] in 1955, who applied perforated belladonna adhesive tape to manually depilated axillary skin. The authors observed lesions at the tape side clinically resembling 'hidradenitis suppurativa' in 3 of 12 volunteers. Histologically, they noted plugging and dilatation of the apocrine sweat duct associated with severe inflammation limited to a single apocrine sweat gland. In this study, which one may consider to be flawed, the authors interpreted their findings as evidence of the apocrine nature of the disease.

How far have we come in our understanding of the disease more than five decades after the study of Shelley and Cahn? In the following, we will review a compiled paper from a group of 14 authors published in the most recent series of Controversies in Experimental Dermatology.[3] The authors were asked by the section editor Ralf Paus to share their viewpoints of what causes 'hidradenitis suppurativa'. There was no consensus, and while – in the midst of the different viewpoints – it may appear that we have not evolved much beyond the knowledge available 50 years ago, there are some silver linings on the horizon. These 'silver linings' are discussed in the compiled paper[3] and are also published in three studies,[4–6] two of which were conducted by contributors to the Controversies series. These three studies will be reviewed, albeit briefly, because they are also discussed in the Controversies series.

Is 'hidradenitis suppurativa' a disease of the hair follicle and, if so, which portion: cycling (stem) or non-cycling (follicular infundibulum or isthmus)? In either case, the term 'hidradenitis suppurativa' would make no sense. Or, is it a process initiated by or centered on the sweat glands in which case the terminology would be adequate? Intertwined with the issue of the anatomical target from which the process starts is the even more pressing question of what precipitates the changes at the morphological substrate, whatever that may be.

It is well known that 'hidradenitis suppurativa' affects primarily obese women[7] in their 30s to 40s. In view of the anatomical predilection of the disease primarily in intertriginous areas, many of the authors who contributed to the Controversies in Experimental Dermatology[3] favor shearing forces and constant friction originating in the large skin folds, especially of obese patients, as one of the precipitating factors. The emphasis is on one because one would expect more patients suffering from the disease, if biomechanical factors enhanced by obesity were the sole culprit. One author from the Controversies series, Jemec,[3] speculated that microtears of the hair follicle may represent the primary event. We ourselves view microcomedones – essentially dilatations of the follicular infundibulum – as one of the earliest pathogenic events and have documented their presence with rupture sites histopathologically,[1] as have others.[8,9] Once microcomedones have developed, the 'fire of

HS [hidradenitis suppurativa] becomes a bit bigger', as stated by a group of authors (Emtestam et al.)[3] participating in the Controversies series. The microcomedones, preceded by hyperkeratosis of the follicular infundibulum, enlarge extensively over time because their content – keratin – is more resistant to being broken down than in non-intertriginous acne. Subsequent rupture, bacterial colonization, sinus tract formation and scars evolve, at which time the process is difficult to contain. The above scenario would make the follicular infundibulum the prime anatomical target, thus rendering the term 'hidradenitis suppurativa' illogical.

In view of 'hidradenitis suppurativa' as a 'playground for the high priests of nomenclature', as paraphrased in the abstract of the Controversies series,[3] it is not surprising that not every author participating in the compiled paper agreed with the above viewpoint. Jean Revuz concluded his contributions with the statement that 'Any pathogenesis scenario, however, that completely discards apocrine glands and their specific distribution as key elements in the development of HS [hidradenitis suppurativa] may soon turn out to have to be discarded itself!' This author speculates that an abnormal secretion of a substance in the apocrine gland may be a triggering factor in the disease leading to morphologically recognizable effects in the acroinfundibulum 'with the responsible gland disguising itself as an innocent bystander upon histology – a perfectly masked "criminal"'. There are currently no papers validating this viewpoint.

If the follicular infundibulum is the substrate in the pathogenesis of 'hidradenitis suppurativa', could endocrine factors apart from biomechanical shearing forces play a role in the disease? This would link the narrow age spectrum of patients suffering from the disease and the frequent obesity into a common pathogenic scenario. Zouboulis pointed out in his contribution to the Controversies series[3] that studies establishing a relationship between 'hidradenitis suppurativa' and hyperandrogenism often did not control for body mass index and the results are contradictory. However, the association of 'hidradenitis suppurativa' with Cushing's syndrome and acromegaly may indicate a role of hormonal factors in the disease process. More controlled studies, however, are missing.

What is the contribution of genetic factors in the disease? Kurzen briefly mentions in the Controversies series[3] that an initial attempt by Gao et al.[10] to localize the susceptibility locus for 'hidradenitis suppurativa' to chromosome 1q has not been confirmed by other groups (unpublished observations according to personal communication by Uppala Radhakrishna to Kurzen).[3] Studies reporting a link between genetic factors and 'hidradenitis suppurativa' refer to the occasional familial clustering of the disease.[11,12] However, these studies are not controlled for other factors likely relevant, at least indirectly for the disease, such as obesity. To date, no convincing and irrefutable evidence of a genetic predisposition to 'hidradenitis suppurativa' has been presented.

Could 'hidradenitis suppurativa' be infectious in etiology? While a bacterial infection is not the primary cause, Kurokawa in the Controversies series[3] proposes an abnormal immune response against bacteria may play a role in the disease process in that patients with 'hidradenitis suppurativa' may respond abnormally to the residential bacterial flora. In acne vulgaris, bacterial superinfection activates the immune system in the lesions via stimulation of Toll-like receptors.[13] Toll-like receptors are a part of the innate immune response to

bacteria. Hunger et al.[4] describe the overexpression of Toll-like receptor 2 within infiltrating macrophages and dendritic cells in lesions of 'hidradenitis suppurativa'. In addition, the authors also report an increased expression of different C-type lectin receptors including the mannose receptor, CD209, a endritic cell-specific lectin receptor, and langerin, which represent constituents of the innate immune response to bacteria. C-type lectin receptors engage very effectively in antigen capture and uptake by macrophages and dermal dendritic cells. The authors speculate that the bacterially induced enhanced expression may contribute to the pathogenesis of the disease, comparable with acne vulgaris. They emphasize a possible cross talk between C-type lectin receptors and Toll-like receptor 2; both are expressed on macrophages and dermal dendritic cells, and the authors speculate that this may contribute to the chronic state of the disease. Bacteria stimulate the production of proinflammatory cytokines in acne vulgaris, and it has been shown that interleukin-1 alpha causes hypercornification of the infundibulum similar to that seen in acne comedones, which can be blocked by the addition of an interleukin-1 receptor antagonist.[14] Thus, bacterial colonization of the follicular infundibulum, facilitated by the occlusive conditions of microcomedones and later sinus tracts, may be crucial in the initial events leading to 'hidradenitis suppurativa'.

Could a disturbed immune system play a key role in the pathogenesis of 'hidradenitis suppurativa'? This was suggested by another contributor, Giamarellos-Bourboulis,[5] who reported a reduction in the percentage of natural killer cells and a lower monocyte response to triggering by bacterial components in patients with 'hidradenitis suppurativa', who also speculated that these changes might be connected to an autoimmune mechanism. Using flow cytometry and enzyme immunoassays, Giamarellos-Bourboulis et al.[5] reported lower numbers of CD3/CD8 lymphocytes in patients with involvement of the perineum compared with controls in contrast to patients with involvement of the breast, which showed higher levels of natural killer cells in the peripheral blood than controls. How relevant these findings are for a possible autoimmune mechanism leading to 'hidradenitis suppurativa' remains to be seen. However, this publication represents one of only a few experimental studies available in the field.

The viewpoint posted by Kurzen in the Controversies in Experimental Dermatology[3] is quite interesting as it references the first study presenting supportive experimental data explaining why 'hidradenitis suppurativa' is so closely linked to smoking.[6] In this highly recommended article, Kurzen et al. used tissue cultures to study the effects of nicotine on skin from patients with 'hidradenitis suppurativa' and compared the effects to skin from normal subjects. They noted a significantly thicker epidermis in the presence of nicotine, which correlated with the production of non-neuronal acetylcholine in the skin, as suggested by an increased expression of acetylcholine receptors. In the epidermis from patients with 'hidradenitis suppurativa', the highest expression of acetylcholine receptors was found around the follicular infundibulum, while in the sinus epithelia, it was only weak, thus providing a possible link with nicotine. While it cannot explain all pathogenic aspects of 'hidradenitis suppurativa', it is an example of a study extending beyond a mere descriptive approach, which yields valuable insight into the disease mechanism by highlighting the role of the non-neuronal cholinergic system in promoting infundibular epithelial hyperplasia and thus follicular plugging.

Do we indeed have to conclude that we have not advanced our knowledge on 'hidradenitis suppurativa' beyond the study of Shelley and Cahn[2] from 1955? The majority of the contributors to the Controversies in Experimental Dermatology[3] view the disease not as a disease of the apocrine sweat gland. In that sense, we have advanced our knowledge but we have not advanced it enough and to the extent that it becomes clinically applicable in the sense of a therapeutic breakthrough. Nevertheless, a continuous effort for the correct understanding of the pathogenic events leading to this devastating disease will have an impact on therapeutic decision making. It is the personal opinion of the authors of this journal review that the still established belief (in our view incorrect) that 'hidradenitis suppurativa' is a disease of the apocrine glands misguided the clinicians (which we as dermatopathologists serve to guide in the diagnostic approach). Hopefully, further research with possible gene expression profiling, as suggested by Zouboulis, will shed more light into the pathogenesis of this enigmatic disease.

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