Gregor B. E. Jemec, Jean Revuz, James J. Leyden (Eds.)

Hidradenitis Suppurativa

Gregor B. E. Jemec Jean Revuz James J. Leyden (Eds.)

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With 67 Figures and 39 Tables

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dedicated to
Borut

Preface

This is the first and most comprehensive book dedicated to the understanding and treatment of hidradenitis suppurativa. The most recent monograph on this disease was Dr Benedek's supplement to Acta Dermatovenerologica in 1957 (1)! The long interval has not been justified by a benign nature or quiet disposition of the disease. This is a common and debilitating disease that significantly reduces the quality of life for patients. In spite of this it has not achieved a deserved level notoriety and scientific interest, but remains an obscure an ill-understood menace to the patients.

There may be several reasons for this neglect. One reason may be that it is has been described as a 'heart sink' disease, both for patients and physicians alike. Patients often find it a debilitating and embarrassing disease with a high degree of morbidity; and at the same time treating physicians generally find it a difficult disease to treat. Patients therefore hide their disease and chose to suffer in silence rather than to seek help. Physicians similarly often adopt a reductionist approach rather than seeking insight in the face of the clinical challenge. Finally, it may be that it is only now that a sufficient college of experts have gathered.

It is therefore our hope that this book will be of benefit to the many patients; and of inspiration and insight to the many different specialists treating the disease. We have adopted an open, exploratory approach to the topic, rather than a normative one. We have invited recognised experts to give their opinion and interpretation of the disease, and left our own point of view to the chapters summarizing pathogenesis and therapy. At points you may therefore find discussions of e.g. apocrine glands with which the editors may disagree, but rather than suppress information we have sought to stimulate and inspire an an open dialogue. The book is intended for both concrete factual information, as well as inspiration for further studies of aetiology, pathogenesis and therapy.

We would like to thank our colleagues for generously sharing their insight and knowledge. We would also like to thank Ms Ellen Nissen for providing expert translation from French, the anonymous patients for sharing their stories and our publisher for a smooth and efficient cooperation.

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Chapter 1

Hidradenitis Suppurativa Introduction 1

Albert Kligman

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At long last, hidradenitis suppurativa, a disease first described a century and a half ago and one of the most devastating among the thousands of dermatologic entities, has finally received recognition by a text dedicated solely to this horrible disorder.

This publication reminds us that this disease, neglected for most of its history, would merit classification by taxonomists as a "nomen dubium et confusum," about which there has been no consensus regarding etiology, pathogenesis, histopathology, bacteriology, genetics, etc.

Major dermatologic texts the world over give rudimentary, incomplete, misleading, even fallacious and contradictory accounts of this baffling, multifarious, polymorphic disorder.

The historicity of hidradenitis suppurativa, which has been described under a variety of latinized names, is in itself a fascinating, convoluted story, demonstrating once again that the only path to enlightenment and the resolution of controversies is through serious basic investigations. It is worth recounting too how patent fallacies can be perpetuated by the pronouncements of influential clinical figures, schooled in the descriptive morphology of dermatologic diseases. All this has thankfully changed owing to investigations by authoritative contributors to this volume.

The disease was named by Verneuil, a French surgeon, who in 1864 held that the primary event in pathogenesis was inflammation of the sweat glands [1]. This concept held sway over more than a century, during which numerous reports were in concordance. It was not till 1939 that Brunsting identified the apocrine, rather than the eccrine sweat glands as the specific target of the disease, although he did not quarrel with the prevailing idea that the primary event was inflammation of the apocrine glands [2]. In a later paper in 1952 [3] he presciently recognized that hidradenitis suppurativa had some similarities to acne vulgaris regarding clinical manifestations. The latter idea was further fleshed out in 1951 by Kierland, also of the famous Mayo Clinic, who perceived that hidradenitis suppurativa was not solely restricted to localization of the apocrine glands. He saw a relationship between acne conglobata and dissecting cellulites of the scalp, which sometimes occurred concomitantly [4]. Later workers confirmed Kierland's concept that hidradenitis suppurativa was an umbrella term encompassing a variety of clinical expressions.

It was Shelley and Cahn's report in 1955 that gave scientific credence to the belief that inflammation of the apocrine glands was the primary pathogenic event [5]. They sought to validate the concept by inducing the disease experimentally, historically a successful strategy embodied in Koch's postulates. They plucked the axillary hairs of 12 male volunteers and immediately covered the area with an occlusive adhesive tape impregnated with belladonna, the latter presumably to suppress secretory activity. In 3 of the 12 volunteers, they histologically demonstrated hyperkeratotic plugging and dilatation of only one apocrine sweat duct in each specimen, associated with a severe inflammatory infiltrate engulfing and destroying the gland. Notably there was no involvement of the surrounding eccrine, apocrine or sebaceous

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glands. They concluded that hidradenitis suppurativa represented an infection of the obstructed apocrine duct by the resident microflora of the axilla in the absence of known pathogens. Their findings were so commanding and persuasive that a host of reports for many years afterwards by many different observers thoroughly endorsed the concept, which was thereby elevated to the status of a dogma.

Interestingly, no attention was paid to an early blunt dissenting opinion in 1957 by Tiber Benedek, a Chicago dermatologist, who opined that the experiments from the famous Department of Dermatology of the University of Pennsylvania School of Medicine in Philadelphia were "poorly conceived" and that the results bore no resemblance to the native disease either bacteriologically or histopathologically, noting also that there was no evidence that the disease had been reproduced clinically [6]. Additionally Xu and Cook's substantial histologic studies 30 years later completely failed to demonstrate keratinous plugging of the apocrine ducts at any stage [7]. Curiously, the prevailing dogma was not weakened in any way by the sharp criticisms.

On the contrary, in 1956, Pillsbury, Shelley, and Kligman of the University of Pennsylvania School of Medicine in Philadelphia proclaimed in their popular 1956 text, *Dermatology* that "hidradenitis suppurativa is a severe, chronic, recurrent suppurative infection of the apocrine sweat glands, resulting from poral closure and secondary bacterial infection" [8]. It was not until decades later that a steady stream of reports in the world literature failed to verify the Philadelphia doctrine that obstructive hyperkeratotic plugging of the apocrine duct was the initiating pathogenic event, or that infection was a common complication [9–11]. The Philadelphia concept has not withstood the test of time and is no longer tenable, as described by later investigators. James Leyden, a younger member of the Philadelphia group, one of the co-authors of this volume, has joined the chorus of dissenters against the views of his eminent predecessors, to which the name of Kligman has perforce been added!

Another of the authors, G.B.E. Jemec, is clearly a leading authority who has published more than a half-dozen reports on the histopathology, bacteriology, and clinical aspects of the diverse manifestations of this polymorphic disease [12–14]. In fact, all of the contributors to this volume have worked in the field, with credible bona fides. Jemec compared 60 consecutive biopsy samples of hidradenitis suppurativa patients with 30 normals, the first large controlled study, which failed to verify the ancient concept.

Some redeeming remarks are in order regarding the Philadelphia triad, Pillsbury, Shelly and Kligman, who perhaps deserve honorable mention for elaborating on Kierland's perceptive observations that hidradenitis suppurativa was more than a disease of apocrine glands but belonged to a family of related conditions [3]. They presented a unifying concept which led them to coin the term "the follicular occlusion triad," relating acne conglobata, hidradenitis suppurativa and dissecting cellulitis of the scalp into one nosologic grouping. This notion has now achieved universal acceptance. Plewig and Kligman added another component, the pilonidal sinus, comprising what is now called the follicular occlusion tetrad [15]. Finally, it was left to Plewig and Steger to coin the term acne inversa to acknowledge that hidradenitis suppurativa, while part of the occlusion tetrad, was a clinical entity, emphasizing its localization to the axilla, anogenital area, and the buttocks [16]. By contrast, acne vulgaris favors the face and trunk. So, hidradenitis logically became the inverse form of acne vulgaris. The first comprehensive account of acne inversa may be found in the third edition of *Acne and Rosacea* by Plewig and Kligman in 1993. The most elaborate account of acne inverse is given by Jansen and Plewig [17].

For the last and final word on acne inversa, the interested scholar should read Plewig's elaborate treatise entitled "Acne inversa, acne keloidalis nuchae, abszedierende follikulitis der kopfhaut" [18]. He goes to great pains to emphasize that acne vulgaris originates in sebaceous follicles while acne inversa invokes terminal hair-bearing follicles.

Attention is called to a fascinating paper by Sellheyer and Krahl with the provocative title "Hidradenitis suppurativa is acne inversa! An appeal to finally abandon a misnomer" in which

they trace out the convoluted history of how concepts of the disease generated conflicting notions of its nature, culminating at last in a consensus [19].

Sellheyer and Krahl are not speaking as historians sitting on the sidelines. They report on what is probably the most extensive histopathologic study ever undertaken. They took 176 biopsy specimens of acne inversa, depicting the evolution of the disease from its earliest stages to its end-stage fibrotic disfigurements, accompanied by abundant high-quality illustrations.

It is a certainty that knowledge about this mysterious, intriguing entity has greatly increased, with few remaining controversies [20]. Nonetheless, it is abundantly clear that many important questions remain to be addressed. Tools for obtaining answers already exist in the modern arsenal of techniques such as molecular biology, bioengineering, imaging, pharmacogenomics, genetics, biochemistry, and still others. The most daunting of the many questions which await enlightenment relate to recognizing the earliest manifestations, which may be mimicked by unrelated disorders, so as to bring to bear treatments which prevent progression to the chronic, disabling end-stage, for which there is no therapeutic option other than extensive surgery.

One has reason to hope that this authoritative volume will not only stimulate greater interest in this disease, enlarging the cadre of investigators, but more importantly to generate the funds necessary to underwrite the research that will usher in a new era that will garner for acne inversa the same level of support accorded to other chronic dermatoses.

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Chapter 2

Verneuil and Verneuil's Disease: an Historical Overview

2

Gérard Tilles

Key points

- Hidradenitis suppurativa is a clinically well described entity
- The classification has been a continuous source of debate for more than 100 years
- The lack of sweat gland involvement has been described in early studies

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As a surgeon Verneuil remains closely connected to the history of dermatology. In fact he described the cutaneous disease subject of this book and was the first official teacher of syphilis and venereal diseases at the Paris Faculty of Medicine at a time when skin diseases were still taught separately.

2.1 Biographical Landmarks of a Surgeon-Venereologist

Aristide Auguste Stanislas Verneuil (Fig. 2.1) was born in Paris on 29 November, 1823. He was appointed Interne des Hôpitaux de Paris in 1843, graduated as a Doctor in Medicine in 1852 (thesis: the movements of the heart) and became Professeur Agrégé at the Paris Faculty of Medicine in 1853 (thesis: the anatomy and physiology of the venous system).

As Surgeon of the Paris Hospitals from 1856, he was officially in charge of the teaching of venereal diseases from 1863. Non syphilitic venereal diseases and primary syphilis were at this time managed essentially by surgeons (for example, Ricord in Le Midi Hospital) whereas dermatologists – notably in Saint Louis – were more involved in the management of secondary and tertiary forms of syphilis.

In fact dermatology and syphilology were first regarded only as complementary specialties. Cazenave – head of Saint Louis Hospital – was in charge of teaching skin diseases from 1841 until 1843, succeeded by Hardy from 1862 [1]. The political events that followed the Franco-Prussian 1870s war encouraged the Faculty of Medicine to accept the creation of Chairs of medical specialties. In this trend, the first Chair encompassing cutaneous and syphilitic diseases at the Paris Faculty of Medicine was founded in 1879 and attributed to Alfred Fournier.

After successive appointments as the head of Lourcine Hospital (for syphilitic women), Le Midi Hospital (for syphilitic men) (1865), Hôpital Lariboisière (1865), La Pitié (1872) and Hôtel-Dieu (1889), and Professor of Clinical Surgery (1872–1889) in La Pitié hospital, Verneuil head-

Fig. 2.1. Aristide Auguste Stanislas Verneuil (1823–1895). Coll Photothèque de l'Académie Nationale de Médecine

ed the first Chair of Surgery at Hôtel-Dieu Hospital (1889–1892).

President of the Société de Chirurgie in 1869 and Charter member of the Congress of Surgery, he was elected as President in 1888. He was also a member of the Académie de Médecine (1869), Member of the Académie des Sciences (1887), and Commander of the Legion of Honour. Verneuil died from a bronchopneumonia on Tuesday 11 June, 1895. His funeral took place on 14 June in a Paris suburb, Maisons-Lafitte [2, 3].

2.2 L'Hidradénite Phlegmoneuse (Verneuil's Disease), Primary Observations

Two French surgeons fathered the description of hidrosadenitis. In 1833, Velpeau (1795–1867) described a phlegmon tubériforme [4] of the axilla, "frequently induced by rubbings and irritations of the sebaceous follicles, by the absence of cleanliness (…) this kind of inflammation which evolution is usually slow can be sometimes quite painful. Its usual ending is suppuration; healing is exceptional." Velpeau described a different clinical aspect named phlegmon érysipélateux, similar to the previous one but always quite painful. "Patients are sometimes afflicted with indurations and tumors that may remain the whole life through."

Velpeau regretted "the ignorance of the authors regarding the awful consequences of these inflammations of the axillae which frequency is probably underestimated, while nothing is more common."

Then, from 1854 until 1865 Aristide Verneuil published a series of articles on skin tumors [5]. Observing the absence of any study on this topic, Verneuil indicated he would deal with those sudoral tumors that may have a surgical interest. Although Velpeau mentioned the origin of the abscesses in the sebaceous follicles, Verneuil taught that Velpeau's tumors had their origin in the sweat glands.

Verneuil admitted he had never observed any patient with such an acute inflammation of the sudoral glands. In fact, the only occasion he had to observe it was on the cadaver of a young patient who died from cachexia. In this observation entitled "inflammations de la région sacrée et fessière, abcès multiples circonscrits et sous cutanés siégeant probablement dans les glandes sudoripares," Verneuil indicated in an extremely precise way that "the buttocks area was scattered with a great number of little escarrs separated from the others (…) moreover a great number of pustules, the size of a pinhead, without any sign of inflammation were disseminated; these pustules were filled by a liquid lifting the epidermis without breaking it. After removing the epidermis, the cleaning of the pustule made perceptible a tiny red hole in which one could introduce a bristle of a boar or a very thin stylet; then one entered a channel of one fifth to one third millimeter crossing the dermis and leading to a subdermal cavity larger than the subepidermal one and filled with the same liquid."

Observing these cavities both linked by a thin channel across the dermis, Verneuil as-

sumed necrosis of the sudoral glands, the pus being excreted by the sudoral duct and accumulating under the epidermis.

Verneuil localized the abscesses in the sweat gland through clinical and micro anatomical observations only. Therefore, he added prudently "I make this observation with reservation 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." However he indicated "to have no more doubt on the existence of a new variety of skin tumors consisting of the hypertrophy of sweat glands." Nevertheless, he added, "I have nothing to say on the aetiology of this disease: the causes of these glandular cysts, the symptoms, the evolution cannot be inferred from such a small number of observations."

In 1864 Verneuil named this disease "hidrosadénite phlegmoneuse" [6]. A few decades later when complementary cases were published, Dubreuilh (Bordeaux, France) considered the word hidradenitis as improper and hydrosadenitis as barbarism [7].

2.3 Further Observations and Discussions in Europe and Overseas

The disease described by Verneuil first received very little attention from dermatologists except from Bazin (Paris) who coined a syphilid under the name "hydradénite syphilitique" [8]. Bazin was actually convinced that this type of syphilid had its seat in the sweat glands. Therefore, he regarded the disease described by Verneuil as of possible syphilitic origin and pointed out that there is no need to make any differential diagnosis between gommous syphilid and hidradenitis suppurativa.

In Vienna, Hebra denied the existence of sudoral tumors considering that, "up to the present time, the sudoriparous glands have not been shown to be subject of any structural affections" [9]. A few years later, Kaposi, Hebra's successor, did not admit the disease as a distinct affection either: "talking about hidradenitis that does not exist as a separate affection seems superfluous" [10]. However, the translators of Kaposi's textbook into French, Besnier and Doyon, although admiring the master of Vienna, did not confirm the Austrian opinion. Although they admit the uncertainties on the histopathological aspects of the sweat glands, Besnier and Doyon insisted on the true existence of the dermal abscesses in the axillary area, which, according to them, represent the most perfect type of the hidrosadenitis described by Verneuil.

In London, Erasmus Wilson [11], a leading light in British dermatology, summarized Verneuil's description and indicated that the tumors, "differ from boils in their deep origin, in the absence of elevation and pointing and also in the absence of core." Wilson considered the affection as caused by external irritation of the skin from neglect of cleanliness, friction, and sweating. At the same time, Radcliffe Crocker described hidradenitis briefly as a type of furunculosis that begins in the sweat coil [12].

Probably the first histopathological study of hidrosadenitis was published in 1889 by Giovannini, who demonstrated the existence of an inflammatory process borne in the sudoral glands that led to their complete destruction [13].

However, despite this publication which seemed to demonstrate the origin of hidrosadenitis, the existence of the disease described by Verneuil was highly questioned until the 1890s. In fact most authors denied it as a separate entity.

From the 1890s on the disease seemed to come into a new era of existence.

In Paris, Barthélémy authored a comprehensive study on the subject. He regarded hidradenitis as a part of the folliculitis that could be generalized or localized in the axillary, labia major or perianal areas. In Barthélémy's article, hidradenitis described by Verneuil disappears and is encompassed in a new nosological framework that includes acnitis and folliclis, terms coined by the author to designate follicular and perifollicular inflammation of unknown origin [14].

At the same time Pollitzer and Dubreuilh [7] (Bordeaux) independently described what they believed to be abscesses of the sweat glands.

In the North American medical literature, the disease described by Verneuil was not men-

tioned until Pollitzer (New York) [15] pointed out the fact that "the disease was in danger of being dropped from our dermatological nosology and even in Paris the affection was so forgotten that in a recent conspicuous example it was not diagnosed," alluding to the cases observed by Barthélémy (Paris) in Saint-Louis Hospital. Pollitzer regarded the observations made by Barthélémy as descriptions that coincided in every detail with Verneuil's first observations.

Pollitzer – who regarded Verneuil's description as "the admirable style of the French clinician" – added that the lesions could occur most commonly in the axilla, anus, nipple, scrotum, and labia majora. He insisted on the inflammation of the sweat glands (hidradenitis) as being the most characteristic pathological feature, "the complete destruction of the affected gland (destruens)."

Dubreuilh indicated that the lesions had their origin in the sweat coil and emphasized the fact that even the authors who considered hidradenitis as a disease of the pilosebaceous follicle did not dare to deny any responsibility to the sudoral glands. Dubreuilh rejected the terms folliclis and acnitis and preferred to keep hidrosadenitis, which, he said, attested to a pathological reality.

In 1902, Török (Budapest) had "the impression that the pathological process is located chiefly in that layer of the skin which encloses the glomeruli of the sweat gland" [16].

In fact the description of the apocrine sweat glands in 1921 [17] established the relationship between this type of sweat gland and the peculiar localization of the disease.

In the 1920s several papers were published in the North American medical literature that emphasized the existence of hidradenitis and its connection to the sweat glands.

On 27 September 1928, Cole and Driver presented at the Cleveland Dermatological Society the case of a "negro boy aged 3 who showed a peculiar folded and thickened axillary skin with small suppurating lesions in various stages." No discussion followed [18].

A few years later, on 20 December 1935, Corson presented at the Philadelphia Dermatological Society [19] the case of a woman aged 22 who presented in the axilla inflamed swelling, discharged sinuses, and scars. The condition had started 6 months beforehand. Corson regarded this case as a typical picture of involvement of sweat glands by pyogenic organisms. Knowles underlined the fact that these cases occurred mostly in women. During the discussion, the participants considered this observation to be the counterpart of the picture presented previously, with similar lesions in both axillae. This case was first thought to be bilateral tuberculosis but inoculations failed to support this hypothesis. Finally the observation was considered to be an infection due to some type of acid-fast organism probably involving the sweat glands.

In 1933 Lane, authoring a résumé of foreign literature, observed that "the disease is not uncommon and it presents a definite clinical picture but it is apparently not very well known probably because it is hardly mentioned in most works on surgery in the English language and it is not mentioned or is only briefly described in many textbooks on dermatology" [20].

Brunsting, presenting complementary descriptions of hidradenitis at the annual session of the American Medical Association [21], regretted that dermatology textbooks paid so little attention to the disease. He described its clinical appearance, insisted on the fact that the disease is characterized by its localization on cutaneous surfaces in which the apocrine type of sweat glands are situated, and emphasized the importance of a surgical treatment in the early forms of the disorder.

A few years later, Brunsting, reviewing the subject at the 71st Annual Meeting of the American Dermatological Association, indicated that hidradenitis, acne conglobata and dissecting cellulitis of the scalp should be considered as "regional counterparts in which the acne process is manifested in its variants and in its more fulminating forms" [22]. He emphasized the fact that these diseases have so much in common that a description of one disorder well fits another: the presence of comedones is common in the three diseases and in fact he endeavored to underline the common clinical and etiological factors of the disorders, namely the acne process. However, many attendees of the meeting denied Brunsting's attempt to group acne

conglobata, dissecting cellulitis of the scalp and hidradenitis.

In fact for the North American School of Dermatology, Verneuil's hidradenitis truly existed as a disease of the apocrine sudoral glands.

Shelley and Cahn's experimental work [23] supported this view. The authors applied a perforated belladonna adhesive tape to one axilla of 12 adults between 20 and 40 years old. In every subject, apocrine anhidrosis developed in taped areas. Three of the twelve subjects developed clinical hidradenitis suppurativa, presenting deep, small, and tender nodules located at the tape site. The biopsy specimens revealed keratinous plugging of the apocrine sweat ducts, dilatation of the duct, and severe inflammation limited to a single apocrine sweat gland unit. The authors also noticed that adjacent glands were entirely normal with respect to the hair follicles, the sebaceous glands, and deeper eccrine glands. They concluded from this study that the nodules clinically observed were simply an inflammatory change which had singled out the apocrine glands and that hidradenitis suppurativa appeared to be a bacterial infection of an obstructed apocrine sweat gland.

2.4 Hidrosadenitis and Acne Conglobata: Controversial Views

In the twentieth century the French School of Dermatology centered the nosological discussion on the connections between acne conglobata (described in 1901 by Spitzer under the name of dermatitis folliculitis et perifolliculitis conglobata) [24] and hidrosadenitis.

In 1904, Audry (Toulouse), authoring the chapter on sweat glands in the prestigious *Pratique Dermatologique*, pointed out the fact that "reading the authors who dealt with this question gave an impression of a complete darkness, distinct diseases being described under a common name." Audry indicated he had never found any convincing evidence of the initial origin in the sweat glands [25].

Thirty-five years later in the subsequent masterpiece of the French School of Dermatology (*Nouvelle Pratique Dermatologique*) Audry could not still "envision to file perianal and perimamelonal abcesses among the idrosadénitis [sic]" [26]. However, for him more consistent probabilities existed for the sudoral origin of the axillary abscesses, despite the absence of any histopathological evidence. In fact he regarded tuberous abscesses of the axillaries as a subcutaneous boil (furuncle).

In 1949, Degos et al. (Paris) presented a case of acne conglobata abnormally localized to the axillaries, perianal area, and inter- and submammary region, sparing the scalp and the back of the neck [27, 28]. For the authors, the observation gave credence to the follicular origin of the so-called hidradenitis.

In fact, Degos insisted on the difficulty or impossibility of establishing a definite distinction between acne conglobata and Verneuil disease. In this respect, Moline (Paris) underlined the fact that "the close relations between sweat glands and pilosebaceous follicles and the consequences of the infectious process made a rigorous distinction between acne conglobata and hidrosadenitis quite difficult. A common understanding of both diseases may be considered" [29].

Confirming the French point of view, Debay (Paris) [30], concluding his work on perineal suppurations, considered that "the same clinical feature can result from three distinct processes: acne conglobata, Verneuil's disease [aetiology adopted by the Anglo-Saxon authors; no valid differential criterion exists between Verneuil's disease and heterotypical forms of acne conglobata) (…)] and the dysembryoplasia whose clinical features are almost identical to those of acne conglobata and Verneuil's disease."

Mouly (Paris) [31] tried to reconcile the French and American views, drawing attention to the fact that French authors essentially knew the axillary features of the disease, whereas the Anglo-Saxon authors described the perineal features extensively. He insisted also on the fact that hidrosadenitis was commonly designated under the name of Verneuil in the English-speaking medical literature. He incited his French colleagues to acknowledge Verneuil's primary work and to definitively coin the disease maladie de Verneuil.

2.5 Acne Inversa, the Last Metamorphosis of Verneuil's Disease?

In 1956, Pillsbury, Shelley, and Kligman brought together acne conglobata, hidradenitis suppurativa, and dissecting cellulitis of the scalp [32] under the name follicular occlusion triad [33], whose common feature was a tendency to follicular hyperkeratinization leading to the retention of keratin products with secondary bacterial infection.

In 1975, Plewig and Kligman [34] added pilonidal sinus to the triad and proposed the term acne tetrad, pointing out the absence of apocrine involvement in hidradenitis suppurativa. More recently, Plewig and Steger proposed designating entities previously named acne triad or tetrad as acne inversa [35].

The fundamental change in acne inversa is the hyperkeratosis of the infundibulum as in acne vulgaris [36]. The authors denied that eccrine or apocrine sweat glands are involved in the pathogenesis of acne inversa. The involvement of sweat glands was regarded as secondary only. More recently, studies have shown that acne inversa is a defect of the terminal follicular epithelium. According to these authors [36], the association of acne inversa with many disorders in which poral occlusion is prominent gives credit to the follicular origin of acne inversa. They insisted that it was necessary to abandon the term hidradenitis suppurativa [37].

As for Verneuil, the original eponym of this long and confused history, he seems abandoned.

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Chapter 3

Clinical Presentation

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3

Key points

- Hidradenitis suppurativa (HS) or Verneuil's disease is a chronic, recurrent inflammatory, painful disease of apocrine-gland-bearing skin
- HS is an overlooked disease that affects a significant number of patients
- Women are more frequently involved: M/F = 1/3
- HS develops in the second or third decade of life
- Typical lesions are deep-seated nodules, sinus tract and hypertrophic fibrous scars
- The two main areas involved are axillae and inguino-femoral zones
- There is an extreme variety in the severity of the disease
- Quality of life is severely impaired

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3.1 Introduction

Hidradenitis suppurativa (HS) is a distinctive chronic disease primarily located to inverse areas of the skin, e.g. axillae and groin. These areas generally may also be said to be apocrine-gland-bearing skin, although the apocrine glands are not primarily involved in the disease. In the early stages the disease is an inflammatory and pustular follicular disease, but subsequently it becomes predominantly suppurative and scarring. In addition to the objective clinical manifestations of the disease, the inflammatory changes and suppuration cause immediate pain, soreness and discomfort to the patients. In spite

of the distinctness of HS it is commonly misdiagnosed and frequently poorly managed, which adds to the burden of this disabling chronic disease, which severely impairs the quality of life.

Epidemiological and clinical observations may be of help, as corroborating evidence, in establishing the diagnosis of HS. Generally, HS develops almost always after puberty, usually in the second or third decade of life. It is not an uncommon disease with a prevalence rate of 1% [8]. Women are more frequently affected than men; the sex ratio is 3:1 [1, 7, 8]. This has led to speculation about the aetiological role of endocrine and behavioural factors, although none of these have hitherto been found to be convincing on closer examination. Epidemiological studies however suggest that tobacco may play an aetiological or more likely a pathogenic role in the disease, as 84% of patients are current smokers [1]. Another frequently suspected aetiological/pathogenic factor is obesity. Being overweight is not uncommon but not a unifying characteristic of the patients either: among the 164 patients of a personal series [1] 20% were overweight and 20% obese (body mass index, BMI, >30 kg/m^2). The median BMI was, however, 23.6 kg/m^2, which may be considered normal. Similarly, another earlier series found no significant deviation from ideal body weight in a series of 76 patients as a whole [6]. It is most likely that these factors play a role as pathogenic elements in the progression of the disease and in the severity of the disease rather than as actual aetiological factors.

3.2 Individual Lesions

3.2.1 Primary (Early) Lesions

Insidious onset with pruritus, erythema and hyperhidrosis has been reported, but such "prodromes" are most likely rare or not noticeable to the patients. Most frequently, the first lesion is a solitary painful, **deep-seated nodule** (0.5–2 cm in diameter), in an area of inverse or apocrine-gland-bearing skin such as e.g. the axilla (see Fig. 3.1a, b). This lesion is round and deep without any "pointing" or central necrosis such as occurs in a furunculosis (it forms a "blind boil"). It may resolve spontaneously within several days – a mean of 7 days is described [12] – or persist as a non-tender, "silent" nodule with subsequent recurrences of inflammatory episodes over weeks or even months without any evidence of suppuration.

Usually the lesion will progress to form an **abscess** which may open superficially to the surface yielding purulent and/or sero-sanguinous drainage. This abscess may fail to open spontaneously and becomes extremely painful, leading to a surgical drainage (see Fig. 3.2). Drainage typically offers temporary relief, but the disease has a strong tendency to reoccur at exactly the same place. The diagnosis is frequently missed at this stage.

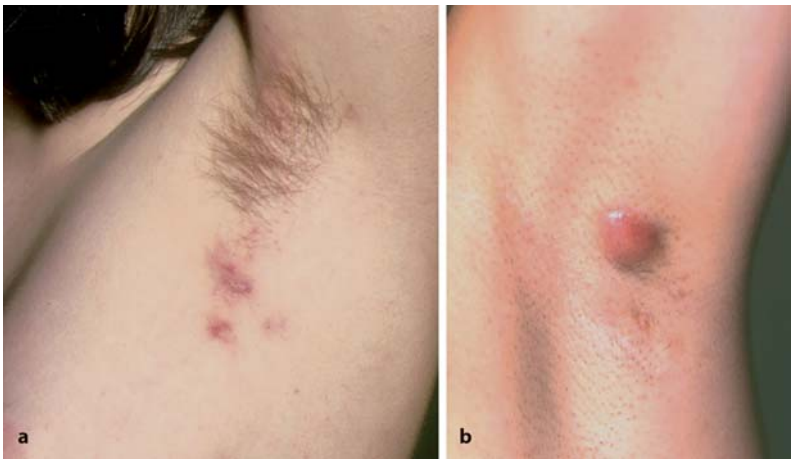

Fig. 3.1 a, b. **a** Early nodule; this lesion is not a "typical deep-seated nodule", which is more palpable than visible; it is a more superficial nodule. **b** Early lesion, inflammation accessible to antibiotic therapy

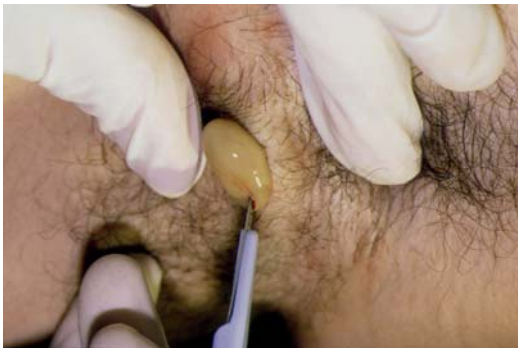

Fig. 3.2. Incision of an abscess yielding pus

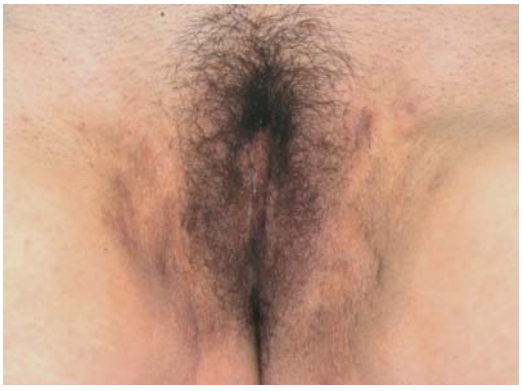

Fig. 3.3. Inguinal hidradenitis suppurativa (*HS*): nodule, closed sinus, comedones; severity: Hurley's I in a quiet period

3.2.2 Secondary Lesions

Chronicity and recurrences are the hallmark of HS. Recurrence at the same site, appearance of new lesions in adjacent skin and coalescence of existing lesions by extension will result in secondary lesions. Fibrosis is another hallmark of the secondary lesions. Fibrosis affects the surrounding skin, and the secondary lesions are therefore thought to perpetuate the disease. Histologically the secondary lesions are characterized by the appearance of **sinus** tracts. Clinically these are persistent for months, or even years, and regularly cause problems to the patient.

This kind of lesion may seem to resolve, only to start draining again after several months of "rest" (see Fig. 3.3). Their potential for resolution is not known, and to the patients they often appear as permanent problems. The sinus tracts are not always palpable, and may only become apparent when an intralesional injection is made and the injected substance appears at a distance from the site of injection.

The draining sinus has a linear or angular shape. At first it is single, then multiple sinus tracts usually appear, with permanent discharge. There is frequently foul odour from Gram-negative colonization (see Fig. 3.4). Because of the chronic inflammation and disruption of the sinus tracts multiple pyogenic granulomas may appear, adding another recognizable feature to the secondary lesions of HS (see Fig. 3.5).

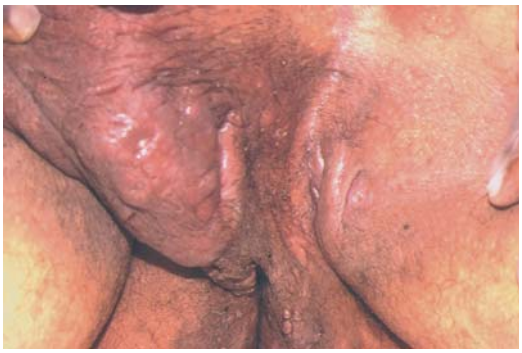

Fig. 3.4. More severe case of inguinal HS with nodules, fistulas, hypertrophic scarring. Severity: Hurley's II–III

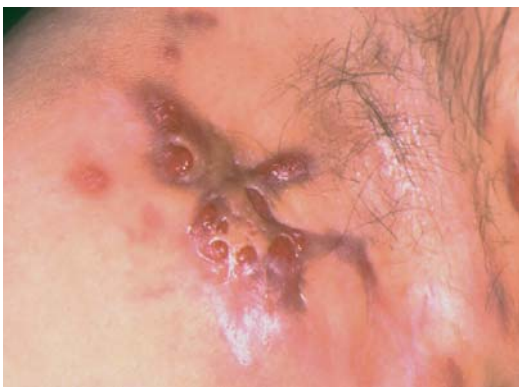

Fig. 3.5. Pyogenic granulomas sprouting from HS sinuses

3.2.3 Tertiary Lesions

The final stage of the disease (Hurley stage III, see below) is characteristic and most often recognized. The chronic inflammation and pain are accompanied by a very peculiar and specific form of **hypertrophic fibrous scarring** leading to indurated plaques in which the inflammatory nodules and sinus remains active (see Figs. 3.6, 3.7a, b). This process may involve the entire zone of apocrine-gland-bearing skin to form a subcutaneous honeycomb-like structure on clinical examination. In more lax, flexural skin (e.g. axillae), this "bridged scarring" results in thick linear, rope-like bands (see Fig. 3.6), sometimes as big as a finger, which are highly characteristic and specific for this disease. When it is severe, such scarring may decrease the mobility of

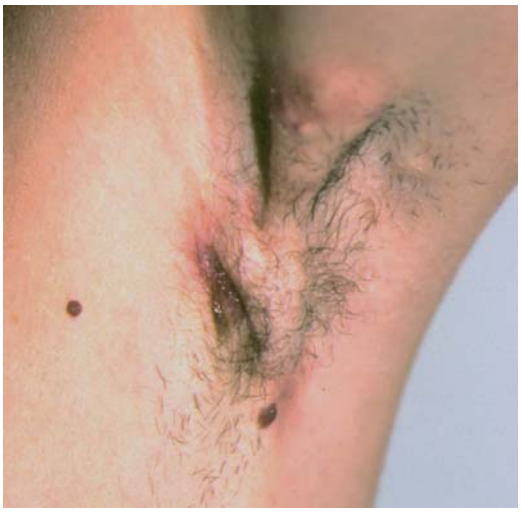

Fig. 3.6. Rope-like hypertrophic scar

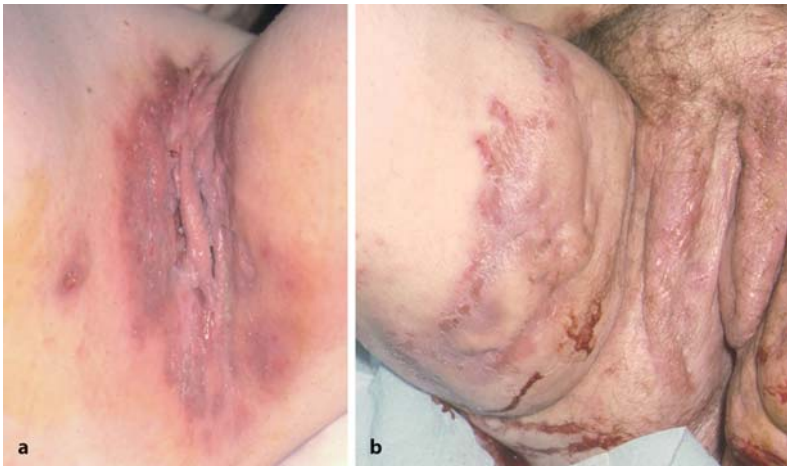

Fig. 3.7. Severe inflamed HS; severity: Hurley's III

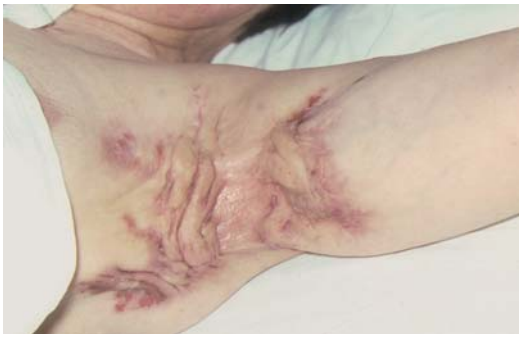

Fig. 3.8. Severe axillary involvement with limitation of arm mobility

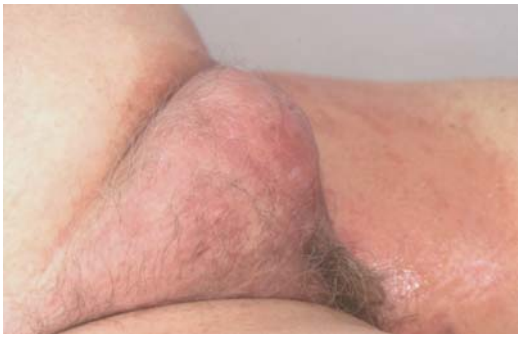

Fig. 3.9. Pubic lymphoedema in HS

a limb, particularly abduction of the arm (see Fig. 3.8) or even produce a lymphatic obstruction with oedema (see Fig. 3.9). It is however of note that lymph node enlargement and/or inflammation is generally absent, except in cases of acute superinfection with lymphangitis.

3.2.3.1 Comedones

Closed comedones ("white heads") are never present in areas of HS. Open comedones ("black heads") are also absent in early disease but may appear in long-lasting HS, usually as double-ended comedones. These may be taken to reflect the distortion and degradation of the dermal architecture caused by the extensive inflammation and scarring of the disease. They are particularly conspicuous in burnt out lesions, presumably when no longer obscured by the active disease (see Fig. 3.10). As in acne conglobata these are tertiary lesions i.e. **"tombstone comedones".** They are present in 50% of patients [8]. Their prevalence does not appear to be affected by either concurrent acne or a previous history of significant acne [1].

3.2.4 Other Lesions

A number of other lesions may be seen in patients with HS. Some of these lesions are clearly follicular and may therefore obscure HS lesions and cause a delay in the diagnosis. Common small **follicular papules and pustules** are frequent in area in both early and late HS (see Fig. 3.11) and may occur isolated in a region not involved by HS [1, 2]. The general prevalence of minor pustular follicular lesions of the skin in not known, but such transient lesions are estimated to be very common. In HS patients such lesions are not uncommon on the buttocks, but they do **not** constitute a diagnostic clue for HS (see Fig. 3.12). Other common findings are the circular depressed superficial scars also sometimes observed on the buttocks of patients. These are most likely secondary to the unspecific elements, and are not a clue for the diagnosis of HS.

In a subgroup of patients, however, cysts occur as a prominent associated finding. These cysts are either white, round 1- to 2-cm smooth elastic cysts grouped in flexural areas, or large

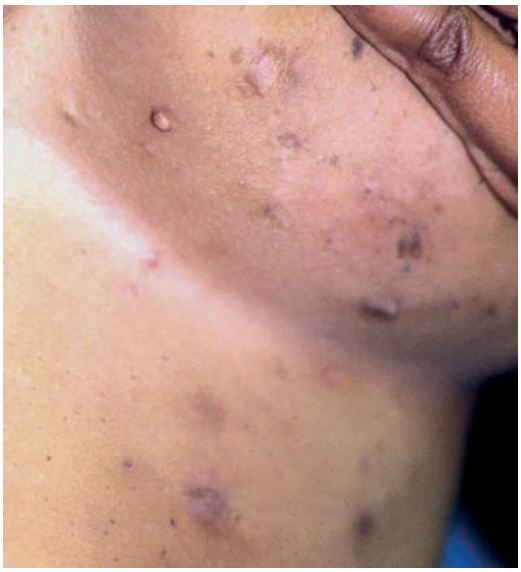

Fig. 3.10. Comedones, black heads in burnt-out lesions

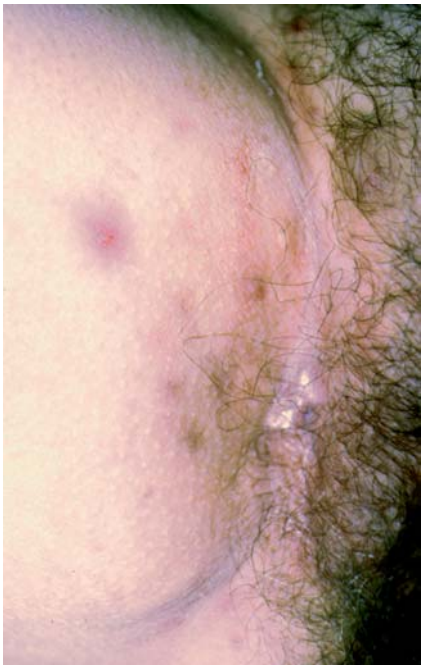

Fig. 3.11. Folliculitis close to HS

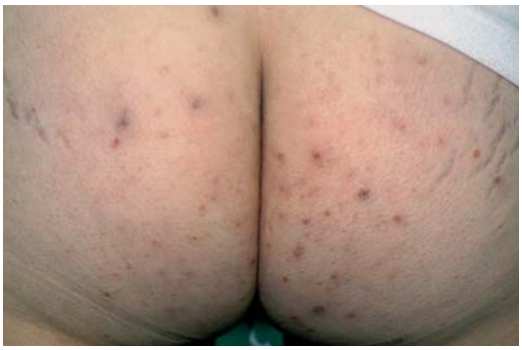

Fig. 3.12. Buttock folliculitis in a patient with axillary typical lesions of HS

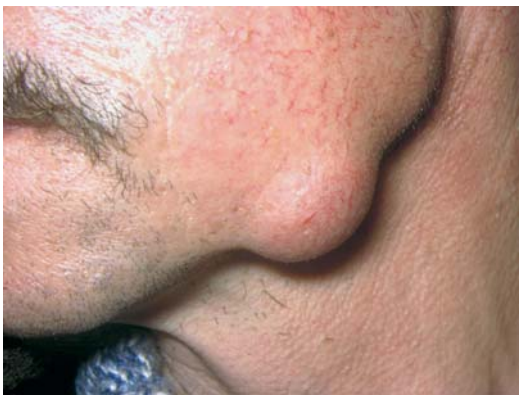

Fig. 3.13. Epidermal (epithelial) cyst

(3–5 cm) epidermal cysts, which can also be observed on the trunk or face of patients with HS (see Fig. 3.13). Clinically, these cysts appear to be associated with primary elements of HS and offer a positive clue to the possible efficacy of retinoids in the treatment. Other lesions such as acne or pilonidal cyst are covered in Chap. 6.

3.3 Topography

3.3.1 Involved Areas

The typical distribution of HS lesions closely corresponds to the anatomical localization of apocrine sweat glands: armpits and the groin. Lesions also occur in a line connecting these two regions passing by the breast and extending to the anal zone.

3.3.1.1 Two Main Zones

The axillary and the inguino-crural zones are the two main areas involved in HS [1, 2, 7]. The diagnosis is often most obvious in the axillary region. Involvement of **axillae** may extend to the lateral part of the chest (see Fig. 3.14) and sometimes achieve connection with lesions on the breast, where they may be misdiagnosed as a breast abscess. Rope-like hypertrophic scarring is particularly prominent in advanced axillary lesions.

Inguino-crural or groin involvement is more frequent than axillary involvement and is especially frequent in women: the inner thighs (frequently), the mons pubis (see Fig. 3.15) and the labia major may be involved. Groin involvement is less frequent in men, and scrotal localization is unusual. Differential diagnoses should therefore be particularly strongly considered for scrotal lesions.

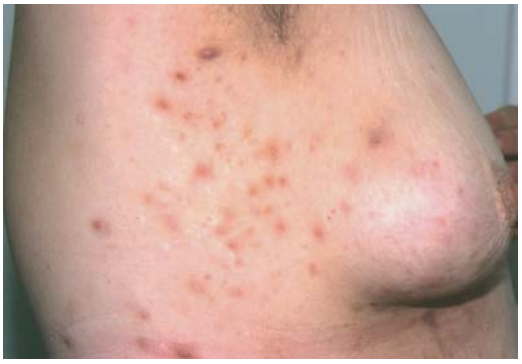

Fig. 3.14. Lateral thoracic extension of axillary involvement

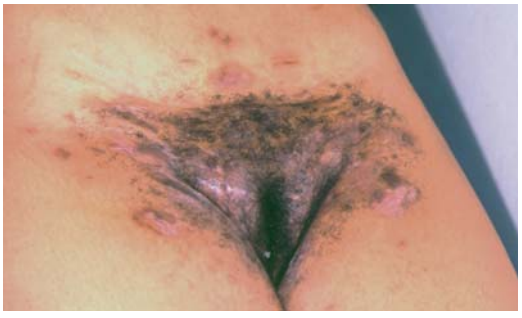

Fig. 3.15. Pubic and inner thigh involvement

In some patients the inguino-genital localization may extend to involve the perineal and perianal area, but in most patients these are clearly separate lesions. Thus, it is important to distinguish between anterior and posterior localizations as their differential diagnosis, prognosis and treatment are different.

3.3.1.2 The Two Less Frequently Involved Zones

The **breast** may be involved in women, particularly the sub-mammary folds, sometimes the inter-mammary fold (see Fig. 3.16) and the areola. These lesions have the same characteristics as HS lesions elsewhere and are, as a rule, easily differentiated from acne lesions. It is a clinical diagnostic aid that comedones are not present in HS.

In contrast, the **perineal and perianal** zones are mainly involved in male patients (see Fig. 3.17). When this zone is the only one involved, HS has to be differentiated from several conditions especially pilonidal sinus and Crohn's disease, see Chaps. 6, 7.

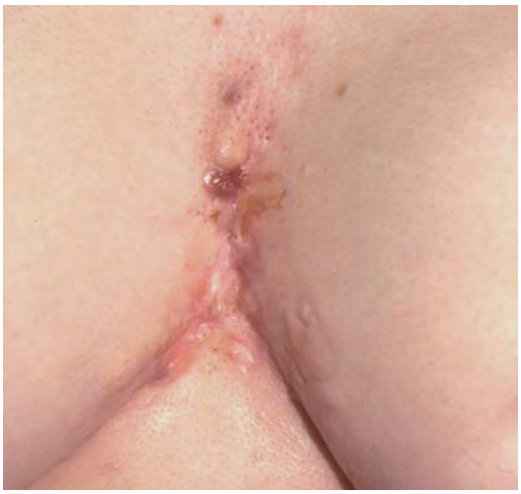

Fig. 3.16. Inter-mammary HS

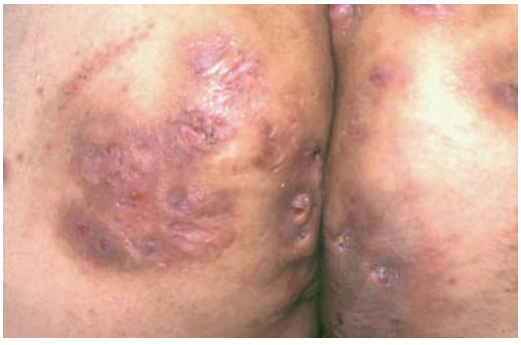

Fig. 3.17. Perianal and buttock involvement

3.3.2 Atypical Localizations – Other Zones May Be Involved

The **buttocks** are one of the most frequent of these "atypical localizations" especially in men. The clinical aspect is sometimes very peculiar: the deep-seated abscesses and sinus are closely associated in a unique lesion slowly extending at the periphery over a period of years (see Fig. 3.18). The lesions may be very large, solitary and very deep. Such single macro lesions may be mistaken for regular abscesses of the muscle or even bone-derived lesions. Lesions of the buttock therefore are easily differentiated from superficial follicular inflammation.

Numerous other localizations have been reported: the nape of neck, the waist (corresponding to the waist band), peri-umbilical lesions, the external auditory meatus, retro-auricular

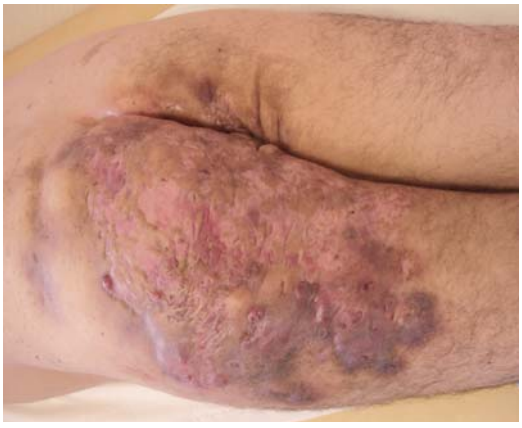

Fig. 3.18. A unique buttock lesion slowly extending peripherally over a period of years

folds and the eyelids. Some of these reports stem from the finding of inflamed apocrine glands, and therefore reflect the mistaken supposition that HS is an apocrine gland disease. These lesions are usually not typical of HS, and their relationship to HS is often at best tenuous. Furthermore, they are infrequent and there is always doubt about whether they are part of the general disease HS. From a disease management point of view it is often more fruitful if they are considered as being diseases possibly associated with HS, rather than as part of HS itself.

3.3.3 Distribution of Lesions

The frequency of each localization is different in men and women [1, 4]. Axillary involvement has no gender predilection whereas genito-femoral lesions are significantly more common in women. In contrast perianal and perineal as well as buttock lesions are significantly more common in men (see Figs. 3.19, 3.20; Table 3.1).

One or several sites may be involved in the same patient, and activity in the sites may vary as well. New regions may be involved at the same time as the disease burns out in regions previously affected. One site may be quiescent, while another experiences a flare. In general, lesions are roughly symmetrical, indicating a systemic disease rather than local infection.

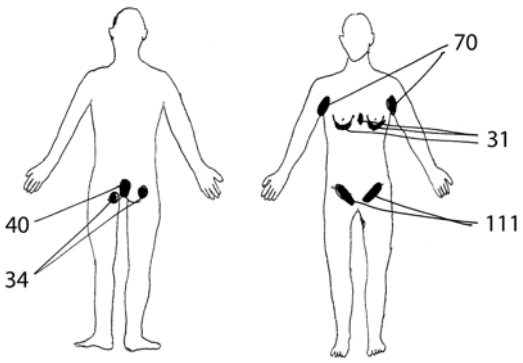

Fig. 3.19. Areas involved in 121 women [1]

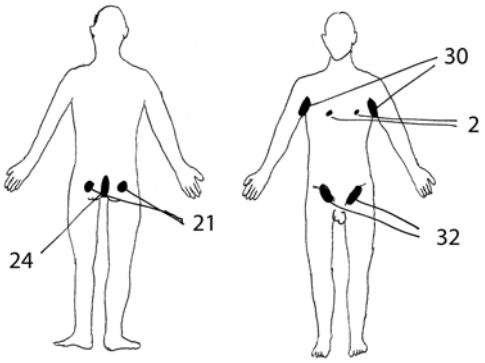

Fig. 3.20. Areas involved in 43 men [1]

Table 3.1. Areas of involvement in men and women [1]

HS patients (n=164, 121 female, 43 male)	Female	Male	p
Axillae	70 (58%)	30 (70%)	NS
Mammary and inter-mammary	31 (26%)	2 (5%)	0.006
Inguino-femoral	111 (92%)	32 (74%)	0.007
Perianal and perineal	40 (33%)	24 (56%)	0.01
Buttocks	30 (25%)	21 (50%)	0.006

3.4 Evolution of the Disease and its Severity

3.4.1 Age at Onset and Resolution

HS develops after puberty, usually in the second or third decade. In a personal series of 164 patients mean age at onset was 22.8 years with extremes of 10 and 57 years (see Fig. 3.21). This finding was similar to those of other series [4, 12]. Genetic factors may affect the onset of disease. Patients with a familial history of HS tend to experience an earlier onset (mean age 20 versus 23 years), although positive bias through over-reporting may occur in families where HS is a communal rather than a personal problem.

The age at onset and age distribution of the cases appear to suggest co-occurrence with hormonal factors, see Chap. 12. Prepubertal cases are rare. In general they are not linked to an

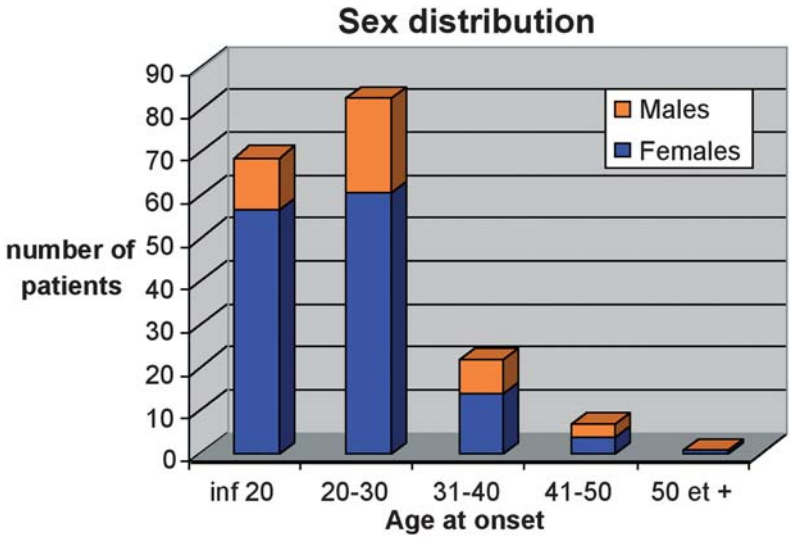

Fig. 3.21. Age at onset in men (n=43) and women (n=121)

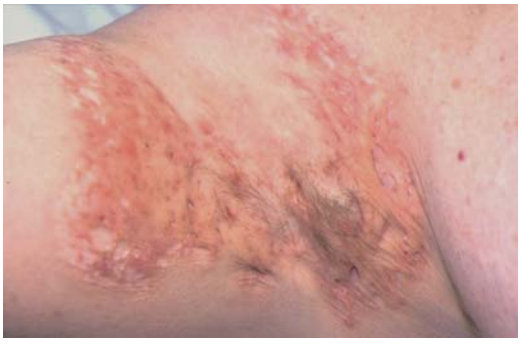

Fig. 3.22. Sequelae of severe HS

early menarche, although cases have been published in which the two co-occur. Similarly, there is a tendency for the disease to burn out after menopause in women. Patients with continuously active disease after the age of 50 (mostly men), however, regularly appear, and for some the disease may even have started at that age.

For most patients the worst years are the first 10 or 15 years after onset [12]. The chance of cure after localized excisions also appears to increase with increasing age of the patient, suggesting that the underlying pathogenic mechanisms abate at an older age [5]. In one series older patients (>40 years) and a patient with a tardy diagnosis however had significantly more severe disease as evaluated by the Sartorius' index [1].

The development of new lesions generally tends to slow down after 50 years, with less inflammation and suppuration but sometimes with severe sequelae with extensive fibrosis and tissue destruction (see Fig. 3.22). It may be speculated that low-grade disease resolves with age, while more severe disease persists or progresses.

3.5 Clinical Course

Chronicity is one of the main features of HS. In a questionnaire survey of 110 patients Von der Werth and Williams reported that in their population – mean age 40 years – the average duration of the disease had been 18.8 years and 98/110 still had active disease [12]. This is indeed a "heart sink" condition for the patient. Furthermore, there is an extreme variation in the severity of HS. In a personal series of 164 patients [1], 76% were in Hurley's stage I, 20% in stage II and 4% in stage III. Most of the patients were therefore early or mild cases where diagnosis remains the most difficult. Premenstrual flare is commonly observed, and may aid the diagnosis of HS. Patient physiology and behaviour may influence the severity of the disease. The BMI does not appear to be an independent risk factor for

disease onset, but may influence the course of the disease. Overweight and obese patients have significantly more severe disease, as evaluated by the Sartorius' index [1]. The smoking of tobacco may, in contrast, be a risk factor for the development of HS. In terms of disease severity, current smokers appear to have slightly more severe disease, but the difference does not reach statistical significance. These factors are of clinical importance to the management of patients.

The disease is highly intrusive in the lives of patients. Von der Werth and Williams reported that 62% of patients acknowledged the presence of permanently painful boils that failed to subside [12]. In our own series 30% of the 164 patients experienced pain more than 15 days a month [1]. It is obvious that the pain, suppuration and repercussions for the patient's social and sex life are responsible for this disease's severe impact on quality of life [11, 13].

General practitioners and most specialists are more familiar with the dramatic aspect of severe disease and remember this picture, thus possibly overlooking the less severe cases that are intermittent, benign or of medium severity. This failure to recognize mild forms of HS explains why the prevalence of HS is generally underestimated.

3.5.1 Intermittent/Benign Course of the Disease

In these forms the disease may manifest itself as episodes of one nodule or abscess followed by a period of remission which may last for several months; during this interval the clinical aspect is normal or one non-tender nodule may persist. The finding of such single nodules on palpation of the affected region aids the diagnosis significantly. The severity at this stage is best evaluated by the number of episode per year and the duration of each episode.

3.5.2 Intermediate Course of the Disease

A large variation in clinical picture can be observed, depending on the several different modes of disease evolution. The disease may be restricted to a single region – e.g. axillary – or expand to all possible areas. The disease severity may also vary. It may be active in all areas or only in one or two areas; and in each involved area the degree of involvement may vary. It may be massive with no normal skin left or the disease may be represented by only one or two nodules or draining sinuses. In a given region, each new attack may be a revival of an old lesion or alternatively the appearance of new nodules and abscesses each time.

If one is to classify the severity of intermediate disease further the number of areas involved, the extent of lesions in each area, and the number of days with pain and/or suppuration are the main factors in the assessment.

3.5.3 Continuous Disease: Moderate, Severe

In more severe cases there are no days off for the patient: pain and suppuration are permanent features of their lives and the disease is relentlessly progressive in one or several areas. Inflammatory nodules rupture externally giving rise to chronic sinuses with intermittent or permanent discharge of a mixture of blood, serous exudate and pus. Who among the patients progresses to this stage of the disease cannot currently be predicted with any certainty. Neither clinical examination nor other tests offer reliable predictive data.

In the extremely severe, untreated cases, one or several affected sites are covered by a mixture of permanently draining sinus and severe scarring with oedema and limitation of mobility. The sinuses can dissect deep into the underlying tissues and go much further than can be estimated clinically. Cases have been reported where an apparent breast abscess proved to be the extension of axillary HS. Ulceration may also occur and burrowing abscesses may perforate neighbouring structures such as muscles or fascia, leading to various fistulas in the genital and perianal region. Fistula formation may involve the rectum, urethra and vagina, and has to be differentiated from fistulas arising within these organs.

In this stage of the disease long-lasting suppuration has previously led some patients to complications such as anaemia, hypoproteinemia and amyloidosis. This kind of wasting syndrome is generally not seen today; however, other complications may occur. Carcinoma may occur, particularly on the buttocks. These cancers appear to have a particularly bad prognosis, possibly because of the local immunodeficiency caused by the long-lasting inflammation and scarring. Except for the common paraclinical signs of inflammation, such as elevated sedimentation rate, low serum iron and elevation of alpha-2 and gamma globulin, the patients are however usually in good general health and without biological repercussions, even in cases of long-lasting severe disease.

The process usually burns out with more or less fibrous sequelae, but the "ending" of the inflammatory process is unpredictable. Frequently menopause brings relief in women, but the association is not constant, and the end may come after or before the menopause. For men it is similarly unpredictable.

3.6 Severity Indexes

Due to the large spectrum of clinical severity, to the severe repercussions on quality of life and to the variety of treatments available, a reliable method for evaluating disease severity is needed. Ideally it should take into account the number, type and size of lesions, evolution, pain and repercussions for quality of life. Such a comprehensive instrument does not yet exist, but two attempts have been proposed to classify patients according to severity.

3.6.1 Hurley's Clinical Staging [2]

This is historically the first classification suggested and is still useful for the classification of patients in overall groups.

- Stage I:
  Abscess formation, single or multiple without sinus tracts and cicatrization.
- Stage II:
  Recurrent abscesses with tract formation and cicatrization. Single or multiple, widely separated lesions.
- Stage III:
  Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area.

Stage I can usually be managed with drugs and stage II patients may benefit from both limited excisions for recalcitrant lesions and drug therapy. Patients in stage III are unlikely to benefit from medical therapy, and should be offered wide surgery.

3.6.2 Sartorius [9]

The need for uniform outcome variables when reporting treatment effects has led to a proposition of a score by Sartorius and co-workers. This classification allows for better dynamic monitoring of disease severity in individual patients, and therefore forms a complimentary system to the Hurley classification.

1. *Anatomical region involved* (axilla, groin, gluteal or other region or infra-mammary region left or right: 3 points per region involved).
2. *Number and scores of lesions* (abscesses, nodules, fistulas, scars; points for lesions of all regions involved: abscesses/nodules 2, fistulas 4, scars 1, others 1).
3. *The longest distance between two relevant lesions*, i.e. nodules and fistulas in each region, or size if only one lesion (<5 cm, 2; <10 cm, 4; >10 cm, 8).
4. *Are all lesions clearly separated by normal skin?* In each region(yes 0/no 6).

A total score or a score by region can be calculated. This score has been assessed retrospectively and should be assessed prospectively in future therapeutics studies.

The Sartorius score lacks a subjective evaluation of the patient, i.e. what is the burden of disease for the individual patient? How much pain

is caused by the disease? And how is the quality of life affected? Pain can be assessed on a visual analog scale (VAS), and the quality of life may be assessed using a validated questionnaire such as the Dermatology Life Quality Index (DLQI) or Skindex. In a study of quality of life in 60 patients a good correlation was observed between the Sartorius score and the Skindex score for quality of life, offering support for the validity of the proposed scores [13].

An "evolutivity score" integrating "objective" and subjective" evaluation of the disease to be used for the management of medical treatments, however, has yet to be constructed.

3.7 Diagnosis

The diagnosis is primarily clinical. No diagnostic paraclinical tests are currently available and a biopsy is rarely required to exclude an alternative diagnosis. Frequently, and especially in benign cases, the diagnosis has to be established primarily on patient history, i.e. more on the questioning of the patient than on objective data gathered by examination. In atypical cases – e.g. buttock involvement alone – the chronicity of the inflammatory and suppurative process is a cornerstone of the diagnosis. In 30% of patients, a positive familial history of HS is found thus helping to establish the diagnosis. This occurs especially among female patients [4].

3.7.1 Diagnostic Criteria

Establishing the diagnosis relies on three main features:

- Typical lesions, i.e. deep-seated nodules (blind boils) and/or fibrosis
- Typical localizations, i.e. armpit and groin
- Relapses and chronicity

Typical lesions can be seen depicted in this chapter. Questions to ask when taking a patient history which may aid the diagnosis are given in Table 3.2.

Table 3.2. Questions which aid the diagnosis of hidradenitis suppurativa

Questions where a positive answer supports the diagnosis of HS:
1. Does anyone in your family suffer from the same symptoms?
2. Do your boils recur at the same spot every time?
3. Do you smoke tobacco?
4. Do you experience a premenstrual flare of your boils regularly?
Questions where the negative answer supports the diagnosis of HS:
5. Do you get random boils on your skin, i.e. on the thighs or abdomen as well?
6. Has the treatment offered by your doctor helped?
7. Do you suffer from infections elsewhere?
8. Do you get a fever when your boils appear?

3.7.2 Delay in Diagnosis

The varying sites involved and the non-specific nature of early lesions mean that patients with HS are referred to many different specialists, including general surgeons, gynaecologists, plastic surgeons, dermatologists, infectious medicine specialists, immunologists, gastroenterologists, proctologists and urologists. This occurs mainly because lesions are most often considered to be common "abscesses" requiring treatment with short courses of antibiotics and lancing, which is an ineffectual form of therapy that must be strongly discouraged.

Unfortunately, the disease is not well known to many general practitioners and other non-dermatology specialists. This may cause delay in the diagnosis and treatment, and consequently in passing information to the patients. In our personal series of 164 patients the mean delay in diagnosis was 7 years with an extreme of 42 years [1]. Failure to recognize HS, failure to give a correct diagnosis and advice on how to manage this chronic disease are therefore common and add to patients' severe distress and impairment of quality of life.

3.7.3 Differential Diagnoses

To the untrained eye the main impression of an acute lesion is the inflammatory, focal process. The most frequent mistake is therefore a failure to recognize what appears as a "common" abscess as a manifestation of HS. Carbuncles, furunculosis, lymphadenitis, infected Bartholin's gland, and the infected epidermal cyst are therefore to be differentiated from early lesions [3].

Carbuncles and furunculosis and other staphylococcal skin infections are often asymmetrical in distribution and by their nature they involve random areas of the skin. Upon examination pathogens are commonly found. Treatment is generally rapidly rewarding when topical and systemic antibiotics are used simultaneously. In addition to identifying the offending pathogens in the lesions, carriers or other sources of infection can often be properly identified and treated. Paraclinically, these patients also show signs of infection, such as elevated erythrocyte sedimentation rates, granulocytosis, etc.

When inflammation is not caused by microorganisms alone, the situation is much more similar to HS, and extra care has to be taken in establishing the correct diagnosis. Epidermoid (or epithelial) cysts, mistakenly called sebaceous cysts, can be present in HS patients; they may exist independently from HS and when in an axillary or inter-mammary localization with occasional inflammation are frequently considered erroneously as HS. The cysts are however most often single and therefore lack the basic symmetry of HS. Furthermore, a primary element may be recognized. The true epidermoid cyst is a superficial firm elastic dome-shaped nodule mobile over the deeper structures. Clinically there may be a central punctum but even in the absence of this, there is often a history of occasional expression of the semi-solid keratinous, foul-smelling and greasy content. Ultrasound examination often reveals a canal corresponding to the central punctum. The identification of the epidermal sack is of course also possible after incision.

True sebaceous cysts form a smooth elastic swelling; they have an oily content. They may be solitary or be part of a steatocystoma multiplex (also called sebocystomatosis). Steatocystoma multiplex may be differentiated from HS by the finding of innumerable cysts evenly distributed over the entire skin, and not only limited to inverse areas. Its association with HS is not well documented.

Late lesions in the ano-perineal location are to be distinguished from other chronic scarring inflammations such as tuberculosis, actinomycosis, cat-scratch disease and lymphogranuloma venereum. For this region an important and difficult differential diagnosis is anal Crohn's disease (see Chap. 7).

In general, the differential diagnoses must be considered, but rarely form true diagnostic dilemmas for the experienced clinician. The co-existence of a number of other diseases which naturally occur when a disease is as common as HS may, on the other hand, present as significant confounders in the diagnostic process, and subsequent nosology of the disease. The co-existing diseases are discussed in greater detail in Chap. 6.

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Chapter 4

Pathology of Hidradenitis Suppurativa

4

Alison Layton

Key points

- HS is a follicular disease
- Apocrine gland involvement appears to be secondary to follicular events
- A lymphocytic infiltrate predominates in early lesions
- Keratin expression suggests that sinus tracts are fragile
- Keratin expression suggests that the outer root sheet may be involved in HS lesions

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4.1 Introduction

There has been significant debate around the pathological features of hidradenitis suppurativa (HS) over the years. This debate focuses on whether the primary event relates to an inflammatory process of the apocrine duct or whether follicular occlusion is integral to the initiating process.

HS was first described as a distinct clinical entity in 1839 by Velpeau [1]. In 1854 Verneuil suggested that the inflammatory changes which affected skin of the axillae, sub-mammary/mammary regions (Fig. 4.1) and perianal areas were linked directly to a disease of the sweat glands [2]. In 1922 a direct association was made between HS and the apocrine glands [3]. As a result of the anatomical distribution and the inflammatory changes noted, the term "apocrinitis" was used as a synonym for HS. This terminology was supported when Brunsting demonstrated the presence of distended apocrine glands containing polymorph neutrophils in the subcutis sections from 16 cases of established HS. He concluded that the disease was an infection that entered the hair follicle duct and expressed its full inflammatory effect within apocrine glands, with further progression occurring via the subcutaneous lymphatic channels [4]. This explanation of pathogenesis was considered the explanation for the increased frequency of HS in African Americans, who have more apocrine glands per unit area of skin.

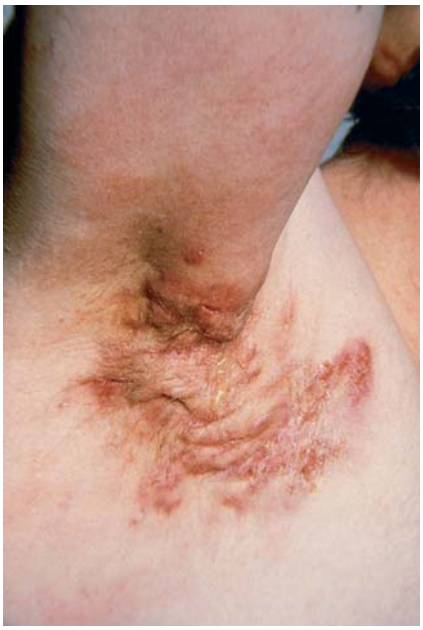

Fig. 4.1. Chronic hidradenitis suppurativa of the axilla

However, in 1955 Shelley and Cahn applied belladonna-impregnated occlusive tape to depilated axillary skin in 12 healthy male volunteers. They produced typical lesions of HS in 3 out of the 12 cases at the sites of application of the adhesive tape. The histological inflammation was confined to the apocrine glands [5]. This work introduced the concept that the initiating event in HS relates to follicular occlusion followed by involvement of the apocrine gland. In 1990, Yu and Cook retrospectively examined axillary skin from 12 patients with established HS [6]. Of the 12 cases, 10 showed squamous-epithelium-lined cysts or sinuses in the dermis all containing keratin and half contained hair shafts, suggesting they were derived from hair follicles. Only 4 of the cases had apocrine inflammation and when apparent this was evident around eccrine glands, hair follicles and epithelium-lined structures. This work suggested that follicular occlusion was a more constant diagnostic feature than inflammation around the apocrine glands.

A further retrospective pathological study of 118 skin specimens from 110 patients suffering from HS demonstrated that follicular occlusion was evident in all of the specimens regardless of disease duration, which ranged from 1 month to 18 years. In contrast, control specimens from axillary and inguinal regions did not demonstrate any follicular occlusion [7]. In the same study, active folliculitis was associated with apocrinitis and apocrine destruction whereas apoeccrine glands, which drain directly onto the epidermal surface, remained intact and showed no evidence of inflammation. This work provided clear evidence that follicular occlusion by keratinous material, with subsequent active folliculitis and secondary destruction of the skin adnexae and subcutis, occurs as an integral step in the pathogenesis of HS.

A further study examining early lesions has confirmed that keratin plugging of follicles and sinuses and inflammation around the hair follicle are frequent features in HS [8]. Clinical support for follicular occlusion includes typical, large, multiple and grouped comedones evident in HS in apocrine sites [9, 10].

Hence, it is now believed that HS conforms to a disorder of terminal follicular epithelium within apocrine-gland-bearing skin but that apocrine involvement does not appear to be a primary event in the majority of cases [11].

4.2 Glandular Elements of the Skin

The cutaneous glands in humans include holocrine or sebaceous glands and merocrine or sweat glands. Merocrine glands are subdivided into apocrine and eccrine glands.

4.2.1 Sebaceous Glands and the Pilosebaceous Unit

The sebaceous glands are an integral part of the pilosebaceous unit and are found over the entire body surface with the exception of the palms and soles. The gland itself is made up of several lobules, which are separated by vascular connective tissue. These lobules all empty into a short duct which then empties into the upper part of a hair follicle at the level of the infundibulum. More than one sebaceous duct may drain into the upper part of the hair follicle.

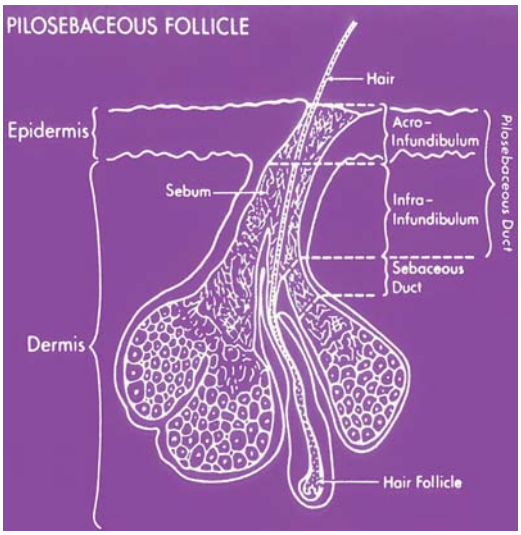

Fig. 4.2. Diagrammatic representation of the pilosebaceous unit

The hair follicle, the hair, the sebaceous gland and arrectores pilorum muscle and (in certain regions) the apocrine glands make up the pilosebaceous unit (Fig. 4.2).

4.2.2 Apocrine Glands

Apocrine glands are found predominantly in the axillary and anogenital regions, although they are also found in the ear canal (ceruminal glands) and eyelids (Moll's glands). They are derived from epidermis and develop as an outgrowth of follicular epithelium. They represent compound sweat glands with a secretory coil that extends deep through the dermis into subcutaneous tissue and drains via a long straight secretory duct, usually into a hair follicle. The function of apocrine glands in humans is not altogether clear but in other mammals they are responsible for sexual attraction, and scent production is responsible for axillary and inguinal odour. They become functionally active and larger at puberty. The secretion is opalescent and malodorous.

4.2.3 Eccrine Glands

Eccrine glands are derived from a specialized down-growth of the epidermis in utero. They represent small tubular structures that drain directly onto the skin surface. They exhibit thermoregulatory control when the body is exposed to a warm environment or during heavy exercise. They are found in all sites of the skin excluding mucous membranes. The sites of maximum concentration are the palms, soles, axillae and forehead.

4.2.4 Apoeccrine Glands

These represent axillary glands in adults and combine morphological features of both eccrine and apocrine glands. A straight intradermal duct opens directly onto the skin surface. The deep secretory component conforms to a dilated apocrine segment whilst proximally the epithelium is compatible with an eccrine derivation.

4.3 Histological Appearance of HS

4.3.1 Early Lesions (Fig. 4.3 a–d)

Follicular hyperkeratosis with plugging and dilatation of the hair follicle is seen as an early event in HS. The follicular epithelium may proliferate or may be destroyed. Inflammation is frequently not apparent in early lesions but perifolliculitis will ensue and the inflammatory infiltrate embraces neutrophils, lymphocytes and histiocytes. Early lesions may show acute inflammation involving the apocrine gland and duct but this is not always apparent and would appear to be a rare primary event [7]. In a study of 36 patients apocrinitis was present in only 5% [11].

Rupture of the follicle spills its contents, including keratin and bacteria, into the surrounding dermis [12].

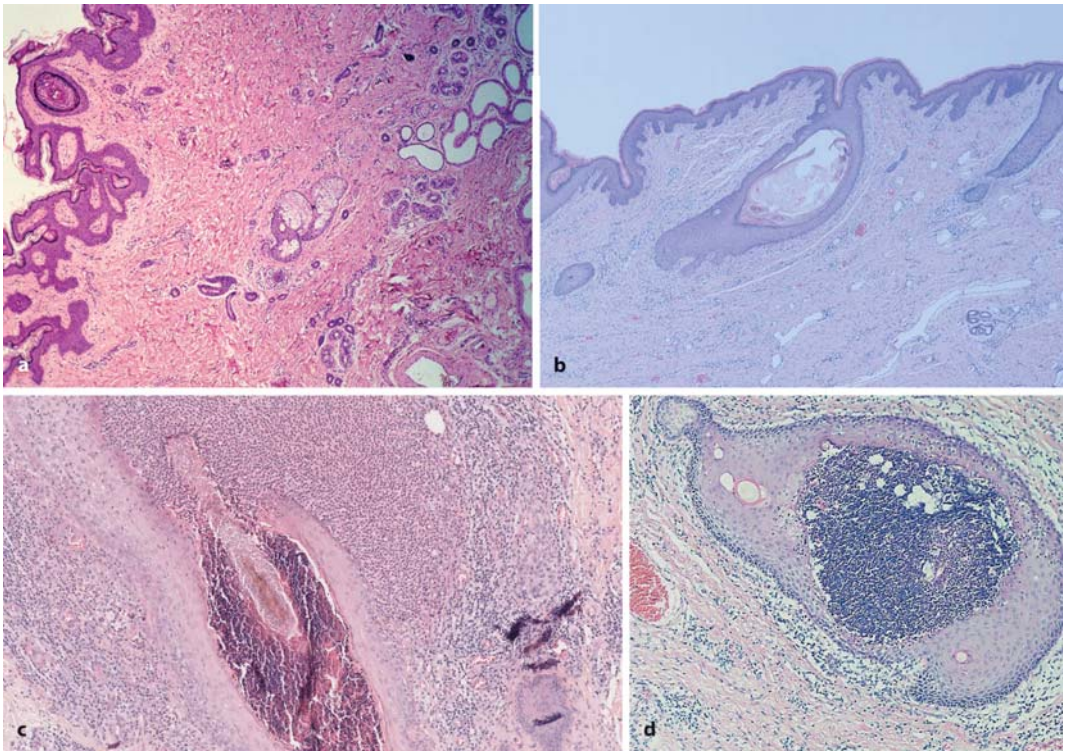

Fig. 4.3 a–d. Early lesions in hidradenitis suppurativa. **a** Acute HS – lower power. **b** Follicular plugging. **c** Folliculitis – dense collection of neutrophils around hair follicle. **d** Acute folliculitis in HS

4.3.2 Established Hidradenitis Suppurativa (Fig. 4.4 a–e)

Biopsy samples from established HS lesions show sinus tracts with marked suppuration and frank abscess formation. The sinuses are lined by stratified epithelium and are surrounded by fibrosis and inflammation. The squamous epithelium extends from the associated follicular epithelium. The inflamed sinus tracts frequently contain desquamated keratin and hair shafts within the dense fibrosis [6]. Within the adjacent connective tissue there is frequently a dense chronic inflammatory infiltrate, which contains histiocytes and giant cells that may be related to keratin fragments. Granulation tissue with inflammatory cells and occasional foreign body giant cells is present in 25% of biopsy specimens [13]. Apocrine glands are generally absent in the affected area but may appear quite normal in adjacent tissue. Extensive fibrosis is frequently seen as a late result in the disease course [14].

Hence it would appear that the involvement of the apocrine as well as eccrine glands represents a secondary phenomenon in HS and results from the inflammatory problem in deep structures.

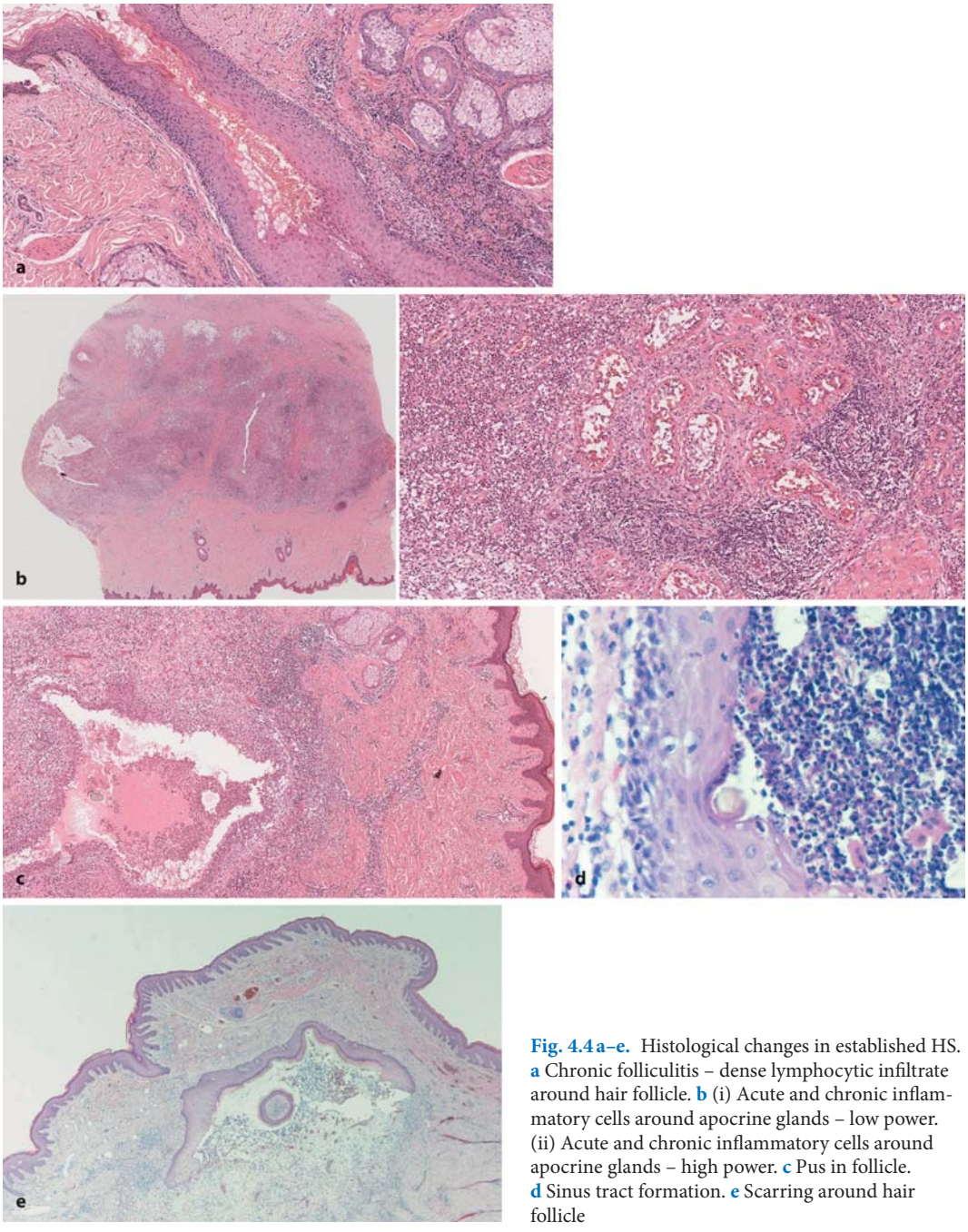

Fig. 4.4 a–e. Histological changes in established HS. **a** Chronic folliculitis – dense lymphocytic infiltrate around hair follicle. **b** (i) Acute and chronic inflammatory cells around apocrine glands – low power. (ii) Acute and chronic inflammatory cells around apocrine glands – high power. **c** Pus in follicle. **d** Sinus tract formation. **e** Scarring around hair follicle

4.4 Immunohistochemistry of Hidradenitis Suppurativa

Immunohistochemical evaluation of apocrine and eccrine involvement in HS has been performed retrospectively on sections of HS from vulval skin. Markers of apocrine differentiation (GCDFP-15, CD15, lysozyme) and eccrine differentiation (GCDFP-15, S-100, CA-19.9, HMB45) were used.

In total 13 cases were examined; the majority of glands identified in the samples from vulval skin were eccrine. Apocrine glands were either not seen or were present away from the area of active inflammation in 10 of the 13 cases. In 2 cases the inflammatory process had apparently destroyed all glands. Follicular obstruction was evident in 11 of the 13 cases. The inflammatory component varied, being severe in some cases to minimal in burnt-out disease. When present, inflammation of glands was only evident in association with poral occlusion, suggesting this was a secondary phenomenon. Fibrosis appeared to correlate with more chronic disease [15].

In a study looking at acute lesions of HS, immunohistochemical examination showed a pattern of lymphocytic predominance suggestive of a cell-mediated response characterized by CD4 helper cells (Fig. 4.5) expressing HLA-DR positivity in keeping with an activated state (personal communication, Dr Julian Barth). The T-helper-to-suppressor ratio was high in the acute HS lesions and in keeping with a cell-mediated response.

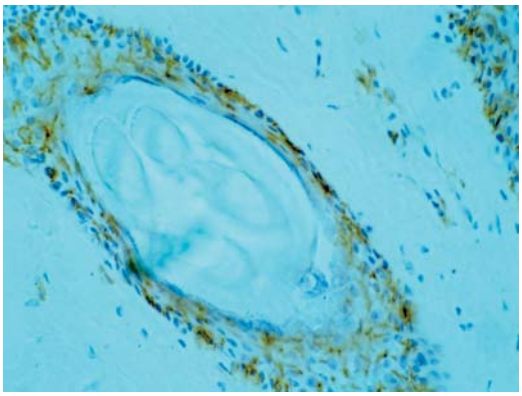

Fig. 4.5. CD4 cells around the follicular duct

These changes mirror those found in experimentally induced early acne lesions [16] where a high ratio of T4 to T8 cells was found at 24 h. Further work looking at time-coursed biopsy samples in acne also confirmed these findings [17].

These identical results in early HS and acne lesions suggest there may be a common mechanism with a type-IV delayed hypersensitivity response to an as yet unidentified antigen.

4.5 Cytokeratin Expression in HS

Cytokeratin (CK) is an important marker for evaluating the origin and state of differentiation of epithelial cells. CK17 (found in normal infundibulum, Fig. 4.6) has been shown to be absent from infundibular-like keratinized epithelium from HS lesions. This suggests fragility of the draining sinus epithelial, which may allow rupture to occur more easily, thus resulting in a subcutaneous abscess. Keratin expression in non-infundibular keratinized and non-keratinized epithelium of HS lesions has been shown to be similar to that observed in the outer root sheath in normal hair follicles [18]. Hence draining sinus epithelium in HS may possess characteristics of undifferentiation and hyperproliferation.

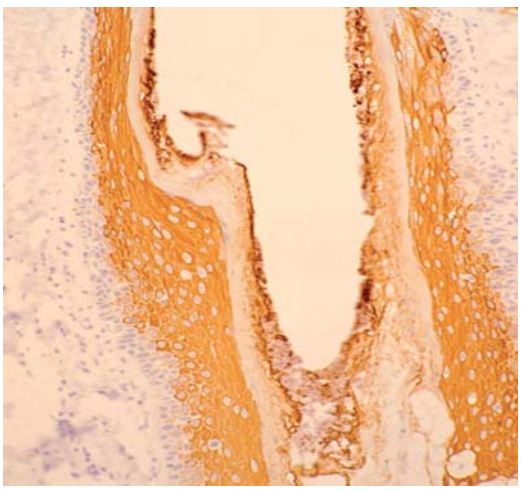

Fig. 4.6. Normal pilosebaceous unit, CK17 was present in suprabasal layers of the infundibulum (original magnification ×100)

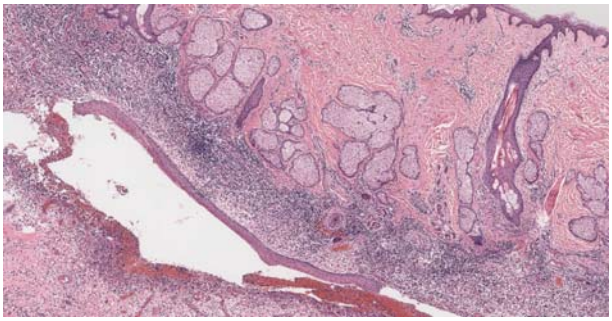

Fig. 4.7. Dissecting folliculitis of the scalp

4.6 Comparison with Other Disorders

4.6.1 Fox–Fordyce Disease

Fox–Fordyce disease has the same anatomical distribution, as well as age and sex incidence as HS. This condition is more convincingly associated with an inflammatory process of the apocrine duct. Of interest there have been descriptions of some cases of Fox–Fordyce disease progressing to HS.

4.6.2 Acne

The pathogenesis of acne embraces increased sebum production, follicular hyperkeratosis, colonization with propionibacteria and inflammatory changes. The sebaceous duct hyperkeratinization is mediated by the production of interleukin-1 alpha (IL1-α) and tumour necrosis factor alpha (TNF-α) by keratinocytes and T-lymphocytes. The result is hyperproliferation of keratinocytes, reduced apoptosis and consequent hypergranulosis. As a result the sebaceous follicle becomes blocked with densely packed keratin and so evolves the comedo. Early comedones show a dilated hair follicle associated with infundibular hyperkeratosis. Later due to rupture an acute dermal inflammatory response ensues. This can be complicated by a foreign body granulomatous reaction. In severe cases abscesses frequently present and cysts and sinuses form. Dermal scarring frequently results in these cases.

4.6.3 Follicular Occlusion Triad

In 1956, Pillsbury, Shelley and Kligman coined the term follicular occlusion triad for the common association of acne conglobata, HS and dissecting folliculitis of the scalp. They proposed that the pathological event unique to each disease was follicular hyperkeratinization [19].

All three diseases, HS, acne conglobata and dissecting folliculitis, represent chronic, recurrent deep-seated folliculitis resulting in abscesses followed by sinus tract formation and scarring. In an actively inflamed lesion the sinus contains hairs surrounded by neutrophils, granulation and scar tissue (Fig. 4.7). In an end-stage lesion there is scarring with patchy inflammation, which may track down a healed sinus at the site of a destroyed hair follicle.

The key histological features of all these conditions are:

1. Poral occlusion of the pilosebaceous units within intertriginous skin sites, especially the axillary area and anogenital regions
2. Secondary inflammation of apocrine glands
3. Inflamed nodules and sterile abscesses, which are followed by sinus tracts, fistulae and hypertrophic scars.

4.6.4 Pilonidal Sinus

In 1975 pilonidal sinus (PS) was reported to belong to the category of follicular occlusion diseases so creating the follicular tetrad [20]. Histopathological findings in PS show follicular

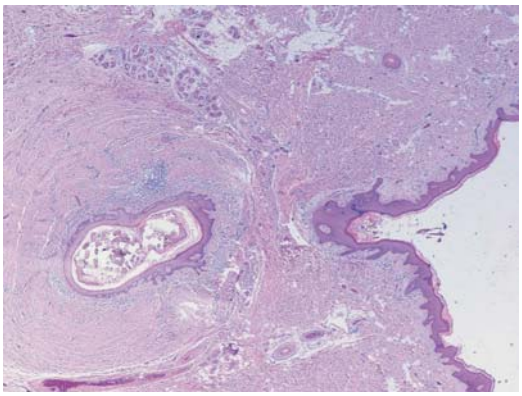

Fig. 4.8. Pilonidal sinus

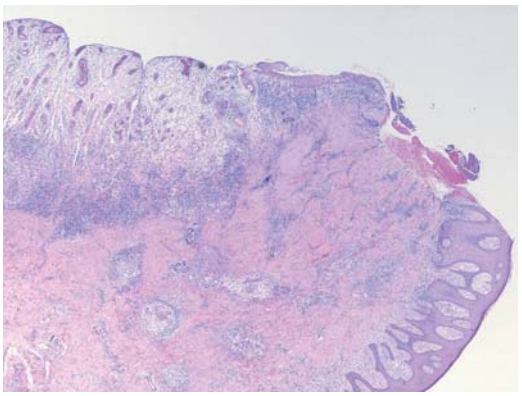

Fig. 4.10. Crohn's disease with epithelioid granulomas

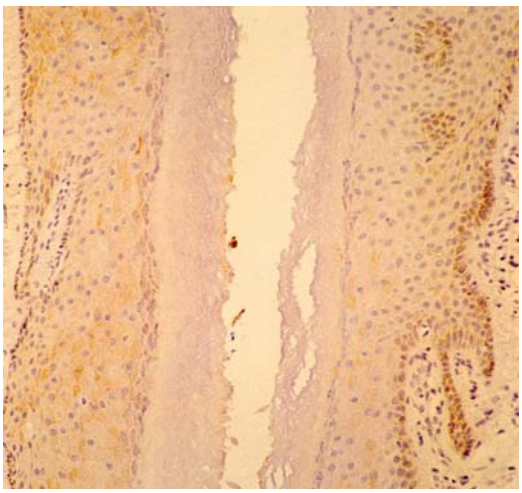

Fig. 4.9. Pilonidal sinus – CK17 was absent in type A epithelium (original magnification ×100)

hyperkeratosis of the infundibulum with plugging and dilatation of the follicle (Fig. 4.8). Superficially the sinus is often lined with stratified squamous epithelium but towards the deeper reaches the wall consists of granulation and scar tissue. The early inflammatory event is perifolliculitis with neutrophils, lymphocytes and histiocytes leading to rupture of follicular epithelium.

In a recent study using immunohistochemistry with six antikeratin antibodies it has been demonstrated that CK expression in PS is similar to that in HS, suggesting that the epithelium may be fragile, hyperproliferative and undifferentiated [21]. Infundibular-like epithelium contained CK1, CK10 and CK14, similar to normal infundibulum, but CK17 was absent (Fig. 4.9).

4.6.5 Crohn's Disease

Differentiating HS from Crohn's disease merits attention. At times these diseases can be clinically indistinguishable and authors have emphasized that although foreign body granulomas are a common finding in HS, the presence of discrete epithelioid granulomas in the dermis away from the site of active inflammation is unusual and should alert the pathologist to the possibility of systemic granulomatous disease such as Crohn's or sarcoidosis [22]. Several authors have reported the co-morbidity of HS and Crohn's [23] (see Fig. 4.10).

4.7 Conclusions

The histological spectrum of HS is broad. The disease appears to be predominantly follicular and apocrine glands appear to be primarily involved in only a minority of histological specimens. Although inflammation does not appear to originate within the apocrine glands, the exclusive finding of the disease within apocrine-gland-bearing skin indicates

an apocrine effect. This diversity of pathological presentation may well explain the therapeutic challenge that this condition poses.

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Chapter 5

Imaging

Ximena Wortsman, Gregor B.E. Jemec

5

Key points

- Hidradenitis lesions extend into the deeper tissue
- Imaging may facilitate the assessment of disease severity and treatment
- Imaging may aid differential diagnosis

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5.1 Introduction

Hidradenitis suppurativa (HS) is a chronic, recurrent and often devastating disease with long-term evolution and severe psychological impact on patients. For practical management of patients as well as for pathogenetic research, skin imaging at a lesser magnification than used for histopathology may also be of interest. In vivo imaging in the millimetre range allows visualization of the hair follicle structure as well as the identification of associated inflammation and the spread of the disease into deeper tissues. This may be of considerable benefit to patients. When abscess and sinus tracts develop in the axillae, the ano-genital region or under the breasts, they may penetrate far from the skin, and may reach distant sites. If this is not properly identified before treatment the presence of such lesions may adversely affect the outcome of, for example, surgery. Similarly, appropriate visualization of the extent of all lesions may help in the planning of surgery; finally, non-invasive visualization of lesions may be used to monitor the effect of, for example, medical therapy. Imaging of this debilitating skin disease may therefore have broad positive consequences for the patients. Two methods have been used for the study of HS: high-frequency ultrasound and MR scanning.

5.2 Ultrasound

Ultrasound imaging is determined by the tissue's physical properties. These physical properties delay the propagation of sound waves. The sound propagation velocity is usually set at 1540 m/s, although it varies slightly in different tissues; for example in the skin it has been shown to be 1580 m/s. The sound is emitted from a transducer, which also serves as a piezoelectric receiver of the reflected echoes, transforming the discrete pressure of an echo into an electric current. The current is then transformed into a surrogate black/white image which can be used for tissue analysis by a trained ultrasonographer.

Ultrasound equipment is widely available in many hospitals, and therefore offers an excellent opportunity for monitoring the subcutaneous spread of HS. More pathogenetic investigations are however also possible. Using high-frequency ultrasound machines, with fre-

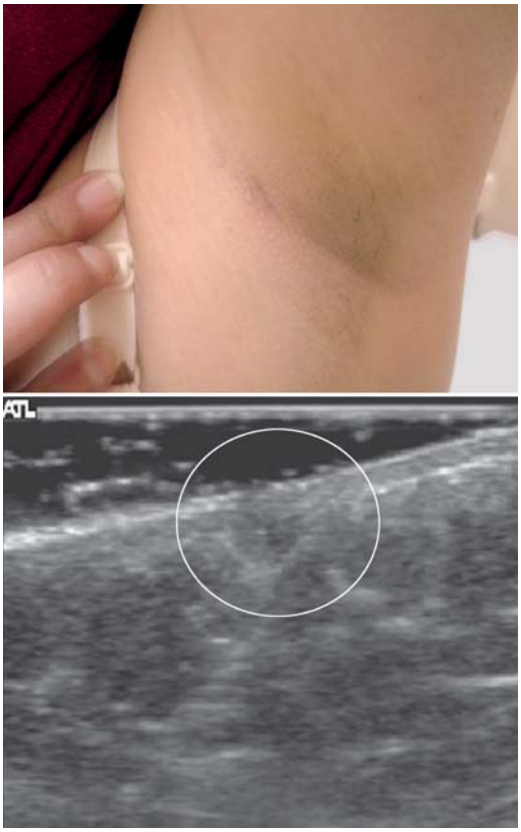

Fig. 5.1. Dermal focal hypoechoic nodular lesion. Hidradenitis patient with subclinical lesion in the axillary zone not suspected by the clinician

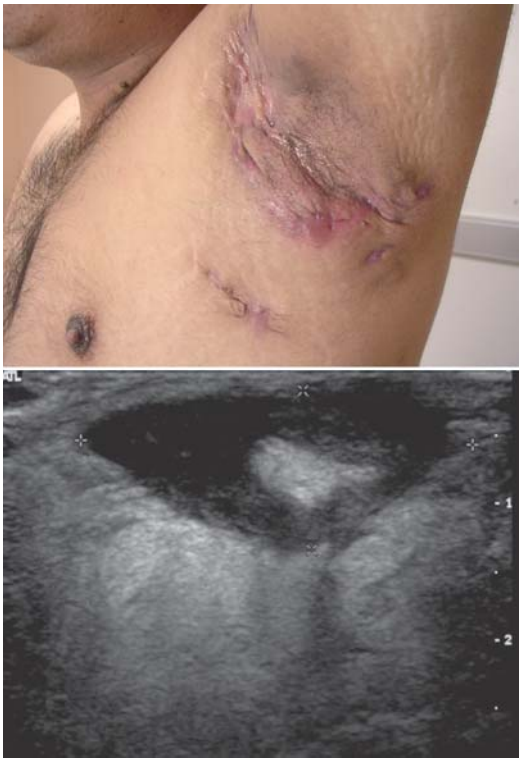

Fig. 5.2. Dermal fluid collection in a patient with extensive hidradenitis lesions

quencies of 15–20 MHz, detailed visualization of hair follicle structure is possible. It has been shown that hair follicles of predisposed regions in HS patients differ from those of healthy controls [1, 2]. The patients appear to have hair follicles with a larger hypoechoic or echolucent diameter at the deeper end, which may reflect either an actual distortion of the follicle lumen or ongoing, subclinical inflammation. In addition to such observations, studies of HS complications or spread of disease are also possible.

To illustrate this point we have studied 5 patients (4 women and 1 man) with HS and 13 healthy control subjects using Philips 5000 and Philips IU 22 Real Time and High Resolution Ultrasound Machines with 15- and 17-MHz frequency linear probes. Images were acquired by a radiologist skilled in the ultrasound examination of skin, and presented as easily detected, characteristic patterns.[1)]

Ultrasound morphological changes of HS can be classified as follows:

- Dermal fluid collections (indicating inflammation)
- Dermal increase of thickness (secondary to inflammation)
- Dermal decrease of echogenicity (oedema)
- Dermal increase of echogenicity (fibrosis or long-term inflammatory changes) showing hair follicle enlargement
- Dermal hypoechoic focal nodular lesions (subclinical)

In particular the existence of dermal hypoechoic nodular lesions (see Figs. 5.1, 5.2) is important in the management of the disease.

1) Data on file

5.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is dependent on the alignment of hydrogen nuclei (protons) in water in a magnetic field. The MR signals that provide the diagnostic information are produced within the patient's tissue in response to radiofrequency pulses, generated by a transmitter coil built into the construction of the magnet. Between the electromagnetic radiofrequency pulses, the nuclei relax and realign releasing energy which is recorded and used for imaging of the tissue. This imaging technique provides good spatial resolution as well as a good ability to distinguish between tissues, and is being extensively used in other areas of medicine.

In HS, MRI has shown lesions with increased skin thickness, induration of subcutaneous tissues and abscess-like lesions [3]. The skin changes are not reported as distinguishable from other those of other disorders, e.g. erysipelas or cellulitis. It may however be useful in the identification of fistulas and deeper sinus tracts and abscesses [4]. Similarly, MRI may give information about the presence of alternative causes of fistulation to the skin, for example, and as such help to identify patients who need different treatment.

Currently there are no commercially available coils specifically for skin imaging, and although these are being developed experimentally, this method appears most helpful when studying deeper or extensive involvement.

5.4 X-Ray Examination

Traditional x-ray examination may occasionally be useful if combined with contrast media. Nadgir and co-workers [5] thus were able to identify perirectal sinus tracts and fistulas caused by HS using a traditional barium enema technique. The use of radiography for the identification of skin lesions or abscesses does not appear fruitful in view of the other techniques available.

5.5 Discussion

The use of imaging techniques is not widely developed in dermatology, most likely because the skin is immediately available for inspection and clinical examination. Imaging techniques, however, do have a role to play in the examination of skin diseases, in particular in diseases that may spread to deeper tissues. HS is an excellent example of such a disease.

Different techniques are available (see Table 5.1) and each method has different advantages, although traditional x-ray examination appears to be less useful than the more modern methods. The use of either high-frequency ultrasound or MRI may be helpful, and the two differ mainly in that high-frequency ultrasound is more readily available and that ultrasound is capable of distinguishing the involvement of superficial skin layers, meaning that ultrasound may be able to detect early changes, even subclinical ones, of the disease leading to earlier diagnosis and treatment.

Ultrasound may be of particular use in the management of HS. The fluid collections found by ultrasound examination are mostly bigger in size and depth than the clinical lesions, and the changes in echogenicity and thickness of the skin layers are also more extensive when compared to the clinical lesions. In addition, ultrasound will often identify nodular hypoechoic (inflammatory) lesions in the skin that are not perceptible to the clinician. In this way the ultrasound examination may give valuable information about the size and severity of the disease in a given patient.

The ultrasound examination is also capable of determining the real magnitude of the dis-

Table 5.1. Imaging of HS. If high-frequency ultrasounda is used excellent imaging is possible of primary lesions and sinus tracts as well, whereas more widely available ultrasound equipment is less well adapted to skin imaging

	Ultrasounda	MRI	X-ray
Primary lesions	++(+)	+	–
Sinus tracts / fistulas	++(+)	++	+
Abscesses	+++	+++	?+

ease and measures the extent and sometimes volume of the fluid collections. Monitoring this disease with ultrasound can therefore show, in an objective way, treatment effects and thereby help guide subsequent steps in medication or surgery. In some cases the fluid collections can also be punctured and drained under ultrasound guidance.

Finally ultrasound may add to our understanding of this disease process. Enlargement of the hair follicles is often seen in areas of the involved zones that are not generally scarred or oedematous, suggesting that it may be an early event in the development of the disease. These observations are in good accordance with earlier studies.

Imaging may also be used in cases where other complications are suspected, and may help to distinguish internal disease such as Crohn's disease from HS. Crohn's disease tracts are different from HS fistulas because they tend to connect with the bowel or anorectal area. In HS the tracts are mostly superficial in location. In patients where Crohn's disease is suspected a computed tomography examination may help to determine inflammatory changes to the bowel. Tuberculosis can also produce sinus tracts and fistulas and they also tend to be deeper in location, near to the bowel or ano-genital area. In this case laboratory tests and chest radiographs could be helpful.

Contrast media ultrasound and molecular imaging using MRI may be a future tool for early identification of inflammatory activity in the skin in asymptomatic or mild cases, since the goal of the imaging methods is to make an earlier diagnosis and improve treatment.

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Chapter 6

Associated Diseases: Causality or Complications?

6

Aude S. Nassif and Gregor B.E. Jemec

Key points

- A number of diseases have been described to co-occur with hidradenitis suppurativa
- Evidence of a true causal relationship between hidradenitis suppurativa and these diseases is weak
- Skin cancer can occur as a rare complication in hidradenitis suppurativa of long standing

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6.1 Introduction

Some patients are less lucky than others and have several diseases at the same time. When this occurs the diseases can be seen as completely separate, or as a reflection of a deeper common aetiology or core pathogenic process. However, keeping in mind Adams's statement that "co-occurrence does not imply association" [1], we have attempted in this chapter to cover all the diseases associated with hidradenitis suppurativa (HS) except for Crohn's disease. It is our hope that by exploring the described associations it will be possible to suggest avenues of future research into the aetiology and pathogenesis of HS. The observations can lead to a segregation of the readership into aggregators and dividers. Aggregators tend to aggregate similar diagnoses into one, whereas dividers split closely related diseases into subgroups. Either approach may be appropriate, providing it is argued from a rational perspective; the argument cannot only be theoretical or practical, but must take the clinical reality into consideration in all its complexity.

We have first described cutaneous diseases including follicular occlusion diseases and pigmentation disorders of the skin folds (Dowling–Degos and Kitamura's diseases), then rheumatologic diseases, neutrophilic diseases and finally cancers (cutaneous and others). By describing the plethora of diseases in which a possible causal association has been contemplated, it is our hope to stimulate the creative curiosity

of the reader, to investigate the possible aetiology and pathogenesis of this disease.

6.2 Cutaneous Diseases (Excluding Squamous Cell Carcinomas)

6.2.1 Follicular Occlusion Diseases

The term follicular occlusion disease refers to a possible common pathogenic mechanism of occlusion of sebaceous or apocrine glands, and diseases included in this term are listed in Table 6.1. An association of these disorders has been described in several patients, suggesting that a causal relationship may be found rather than mere co-occurrence. It has therefore been suggested that the association of HS, acne conglobata (AC) and dissecting folliculitis of the scalp should be named follicular occlusion triad. Acne tetrad includes pilonidal cyst in addition to the three aforementioned components. The actual evidence in favour of such aggregation is however predominantly morphological.

Epidemiological studies raise doubt about the general value of these observations (see Chap. 8). They have failed to support it and clinical experience also suggests that these diseases are not generally associated with HS. Acne vulgaris (AV) appears to be uncommon in HS patients, and while patients may display AC, clinical experience suggests that the two diseases are separate as they react very differently to therapy. The epidemiology of these diseases is also different. The age and sex distribution differ considerably between AV and HS, while the other diseases are both much more rare and less investigated. HS is more common in older persons and women, while AV is more common in younger men. Similarly, *Propionibacterium acnes* and seborrhoea, which are central factors in the development of acne, do not appear to be prominent in HS. In relation to the pilonidal cyst, the abundance of hairs found in these cysts and their solitary and restricted distribution are obvious differences not only between HS and pilonidal cysts, but also between pilonidal cysts and various forms of acne.

The diseases included in the acne triad/tetrad have many similarities, but also profound differences. Our current understanding of the pathogenesis of these diseases, their topographical distribution and their clinical responses to treatment (see Table 6.2) all point towards differences, while the epidemiology points towards significant differences. Therefore, occasional association may well be due to co-occurrence rather than a truly common pathogenic mechanism or a gene linkage.

Table 6.1. Follicular occlusion diseases

Hidradenitis suppurativa
Acne vulgaris (AV)
Acne conglobata (AC)
Dissecting cellulitis of the scalp or perifolliculitis capitis abscedens et suffodiens
Pilonidal cyst

Table 6.2. Treatment options in follicular occlusive diseases. (*?* Unknown utility, – not useful, +[a] useful in selected cases, + useful, ++ somewhat useful, +++ very useful)

	Surgery	Retinoids	Tetracyclines and macrolide antibiotics	Immunosuppression
Hidradenitis suppurativa	+++	+[a]	++	++
Acne vulgaris	+[a]	+++	+++	+[a]
Acne conglobata	+	+++	++	+
Pilonidal cyst	+++	*?*	?	–

6.2.1.1 Acne Conglobata

Acne conglobata (AC) is a disease attributed to an occlusion of sebaceous glands by a process of keratinization. This occlusion can be responsible for secondary sebaceous inflammation. Clinically, the patient presents with comedones, cysts, abscesses and draining sinus tracts, mainly located on the trunk and buttocks, but the face, neck and extremities may also be involved. In the literature, several cases of so-called AC may very well in fact be HS, such as in Whipp's two familial cases of fatal squamous cell carcinoma, in which a 56-year-old woman had suffered from "widespread abscesses predominantly affecting the buttocks, *AXILLAE* and back" [3]. The question of an association between AC and HS arises. In contrast to HS, AC is predominant in men [2]. It is however also highly inflammatory, starting in early adult life with an important tendency to scarring, which in AC is sometimes keloidal. Oral isotretinoin represents a major therapeutic improvement in the treatment of this once disfiguring disease. The drug is considerably more effective in clinical use than earlier drugs such as tetracyclines, but treatment requires high dosages of up to 2 mg/kg per day for months [2]. Immunosuppressive therapy is also indicated when highly inflamed lesions are present. Malignant transformation into squamous cell carcinomas has been reported, similar to other long-standing inflammatory states of the skin such as ulcers [3].

Evidence for a possible causal association is however not strong, and epidemiological studies have failed to support a fixed relationship to cancer. Besides publications mentioning case reports of AC [4–15], it has been stated that it is quite common to find a medical history significant for acne vulgaris requiring isotretinoin in HS patients [16]. The level of evidence is therefore at case-story level or lower. Unfortunately, even though isotretinoin can provide long-lasting remissions and possibly even cure AC, its efficiency against HS is usually minimal. Reports have suggested the efficacy of etretinate or acitretin on both HS and AC, but systematic evidence is lacking [13, 17–19]. However, even in these published cases a relapse of HS occurred between 4 months and a year after stopping retinoid treatment (see Chap. 17).

6.2.1.2 Dissecting Folliculitis of the Scalp

A synonym for this entity is perifolliculitis capitis abscedens et suffodiens. This disease shows considerable geographical variation and most often appears to affect Afro-Caribbean male patients. It usually starts during early adulthood. It has been described in women and girls [20] as well, and familial occurrence has also been documented [21]. An association with acne is reported in 30% of cases [22]. The disease is however uncommon and only a few cases have been reported in the literature making it difficult to establish reliable arguments for an association [20].

Clinically, dissecting folliculitis of the scalp is characterized by peri-follicular pustules, nodules, abscesses and sinus that progressively evolve into scarring alopecia. The clinical picture is often complicated by a keloid tendency [4, 9, 15, 23]. The course of the disease is chronic and relapsing. Squamous cell carcinoma may arise in chronic relapsing lesions and has a recognized metastasizing potential. Death from metastatic carcinoma has been described in one patient [9].

Treatment is generally not rewarding. Antibiotics are commonly prescribed, and combination therapy using rifampicin and clindamycin has been advocated [24]. Tetracyclines in acne doses are usually not effective, whereas some relief may be gained from anti-staphylococcal medicines such as dicloxacillin in long-term therapy (authors' personal experience). Isotretinoin is occasionally (rarely) helpful at a dosage between 0.67 and 1.0 mg/kg per day when prescribed for several months [25–29]. Topical isotretinoin has also been reported to be efficient [22]. Alternatives include zinc [30], systemic or intralesional corticosteroids, surgical excision and skin grafting [29]. X-ray therapy is no longer recommended because of its carcinogenic risk. Both CO_2 laser [31] and 800-nm lasers [32] have been used in a severe case of dissecting cellulitis of the scalp. More recently, long-pulse non-Q-switched ruby laser has been reported as efficient in three patients [33].

In contrast to acne, the tendency for scarring and the recalcitrant nature of this disease bear clear similarities to HS. In the absence of actual genetic classification, the absence of specific

epidemiological data and the relative rarity of the two diseases, however, make actual assessment difficult.

6.2.1.3 Pilonidal Sinus

Many HS patients mention previous surgery for supposed pilonidal sinus, with a tendency to recur several times. Clinically it is very difficult to be sure that these "pilonidal sinuses" are not in fact localized HS. It is particularly difficult to distinguish the two if histopathology has not been performed and if the patient keeps having abscesses in the gluteal cleft. The differential diagnosis is further complicated by the fact that pilonidal sinus is most often treated by surgeons, whereas HS is treated by dermatologists; and the diagnostic criteria and specification may therefore differ by tradition and training.

The clinical picture is identical to a flare of HS, except for the strict localization to the gluteal cleft [10, 34]. Histologically the identification of a substantial accumulation of terminal hair characterizes the pilonidal sinus. In contrast, terminal hair is not very frequently observed in of HS lesions, and when it occurs it usually just shows only as small fragments. Histology is however not regularly done on these lesions, and it is therefore not easy to find an estimate of the true frequency of the possible association between HS and pilonidal sinus. In addition to the histological differences and topographical limitations, the solitary nature of pilonidal sinuses also contrasts with the multifocal nature of HS.

Mechanical strain has been implied as part of the pathogenesis of both diseases, but no conclusive experimental evidence has been presented yet.

6.2.2 Pigmentation Disorders of the Skin Folds: Dowling–Degos and Kitamura's Diseases

Dowling–Degos disease (DDD) or dark dot disease and Kitamura's reticulate acropigmentation are both rare pigmentation genodermatoses that have been described in association with HS.

DDD was first described by Dowling and Freudenthal in 1938 [35], then by Degos and Ossipowski in 1954 [36]. It is characterized by a reticulate pigmentation of the flexures with prominent comedo-like lesions and pitted scars [37–56]. The disease runs in families, it has a genetic autosomal dominant transmission [42, 44] but it may be more prominent in women. DDD, usually localized in axillae, neck and groin, may occur during childhood or early adulthood and may extend progressively. Also noteworthy are the pitted acneiform scars around the mouth present in most of the patients described in the literature.

Pathology shows thin branching pigmented epidermal strand-like proliferations arising from the lower border of the epidermis and the walls of the follicles. The principal differential diagnosis is acanthosis nigricans but the presence of comedo-like structures and the pathology can make the difference. Only two therapeutic options have been proposed: topical adapalene [55] and Erbium YAG laser [56].

Kitamura's reticulate acropigmentation (KRA) is another rare genodermatosis. This reticulate, slightly depressed pigmentation affects the extensor surfaces of hands and feet, occurs during childhood, and it is often associated with milium-sized keratotic papules or simple breaks in the epidermal ridge pattern on palms and fingers. A few families have been described in whom some members show features of KRA and some patients have features of both DDD and KRA diseases [36, 38, 39, 42–45]. Crovato and other authors have therefore suggested that these disorders of pigmentation are two different clinical expressions of the same nosological entity.

Some patients are reported as having only DDD or only KRA while others have an "association" of HS and a pigmentation disorder. In most of these observations, patients' pigmentation phenotype is not reported and one could wonder whether this abnormality is not more common in people with a dark skin colour. This pigmentation may be the result of post-inflammatory pigmentation after bacterial infections or after the frequent inflammation of the folds as seen in HS. The specificity of these signs would therefore appear to be poor. The association is not well supported by epidemiological

studies either. It is fair to ask questions such as: "How often – in our everyday practice – do we see hyperpigmentation in axillary and other folds?" and "How often do we report it?". The answers are most likely "Very often" for the first question and "Never" for the second one for most dermatologists. Data are therefore lacking to establish the likelihood of a causal relationship between these rare diseases and HS. The likelihood of a causal relationship is nevertheless estimated to be low.

6.3 Rheumatological Disorders

Inflammatory dermatoses such as psoriasis have well-known rheumatological associations and often lead to collaboration between dermatologists and rheumatologists for the benefit of the patient. Similarly pustular diseases have well recognized rheumatological aspects, e.g. SAPHO syndrome, where SAPHO stands for the combination of synovitis, acne, pustulosis, hyperostosis and osteitis. The association between HS and rheumatological disorders has been less well studied, although a better understanding of it may add significant information about the pathogenesis of HS.

6.3.1 Clinical Picture

Most reported cases describing rheumatological complications/associations with HS involve black subjects [4, 11, 12, 15, 58, 60, 62–65, 67]. Three different types of manifestations can be observed (see Table 6.3). These patients are HLA B27 negative, and aspirate from the involved joints, when they are performed, are always sterile. Rheumatoid factor and anti-nuclear antibodies are also uniformly absent [62].

6.3.2 Radiographic Features

Erosions are common, involving the joints of hands and feet and medial malleoli; other abnormalities include periarticular osteoporosis, loss of cartilage in wrists, periosteal new bone formation, hyperostosis and diffuse demineralization. In the axial skeleton, sacroiliitis (unilateral or bilateral) syndesmophytes, squaring of vertebrae, erosions and sclerosis of vertebrae may all be observed. Some patients even had asymptomatic roentgenographic changes compatible with sacroiliitis [12].

Table 6.3. Rheumatological manifestations of HS

Axial arthritis with predilection for the sacroiliac joints and lumbar spine. Some cases may present as ankylosing spondylitis
Peripheral arthritis of large joints, usually an oligoarthritis, less commonly a polyarthritis. Peripheral joint involvement consists of symmetrical or asymmetrical erosive arthritis of the hands, wrists, knees and ankles and periosteal reaction involves the phalanges and tibia
Enthesopathy, which is inflammation at the site of ligaments and fasciae insertion over the bone. The most common localizations are the so-called sausage digits (dactylitis), heel pain (plantar fasciitis) and swelling of the Achilles tendon

6.3.3 Treatment

There seems to be a general agreement in the literature that stabilizing HS is probably helpful for stabilizing rheumatological manifestations co-occurring with the disease, and in some patients treatment with antibiotics or surgery for HS or both has resulted in a dramatic improvement in rheumatological symptoms [57, 62, 63]. These observations strongly suggest the interdependence of the two diseases and argue against simple co-occurrence.

Maximum control of cutaneous HS is therefore recommended in all patients with associated rheumatological disease. For the rheumatological complaints, different treatment modalities have been proposed, starting with simple anti-inflammatory drugs, giving some relief, sometimes intra-articular corticosteroid injection [7], or systemic steroids for resistant cases [4, 11]. One isolated case of efficiency of isotretinoin (1 mg/kg per day) has been reported, again supporting the causative role of skin changes [15]. D-Penicillamine alleviated peri-

pheral arthritis symptoms in one patient from Rosner's series [11] but it had no effect on the axial involvement. Sulfasalazine allowed discontinuation of systemic steroids in one patient [4]. More recently, one case of HS associated with Crohn's disease and spondyloarthropathy responded to anti-tumour necrosis factor (TNF) therapy [65].

6.3.4 Mechanisms

Numerous non-specific rheumatological abnormalities have been described in co-occurrence with HS, involving the axial and peripheral skeleton, but the majority of HS patients do not show any rheumatological signs. Although convincing cases have been presented, arguing for the interdependence of skin and joint disease in HS, we are more inclined to think that these manifestations may be an indirect consequence of HS on genetically predisposed individuals, i.e. patients have a rheumatological "susceptibility" rather than a true common pathogenic mechanism.

It is interesting to note that arthritis is almost always reported after the beginning of HS, and only occurs when the disease has lasted for several years. One explanation could be that immunological mechanisms against the different auto-antigens present in the chronic HS lesions provoke rheumatological symptoms. For example, circulating immune complex deposits might be responsible for the joint involvement, which is a well-known mechanism in reactive rheumatological diseases. Some publications support this hypothesis because of the presence of circulating immune complexes or cryoglobulinemia [7, 11, 12, 58, 59, 60, 61]. However, investigations in these patients have not been systematic and similar in all reported cases. Some authors do not mention looking for immune complexes, while others do not find them even though they looked for them. Immune complex deposition cannot therefore explain all the cases. Hellmann gives some interesting hypothesises [56] to explain these rheumatological manifestations.

First, is an infectious localization of a germ coming from HS lesions through haematogenous spread. However, culture of synovial aspirates was negative in all the patients who underwent this test. The following mechanisms have been proposed:

- A bacterial fragment could share a common antigenic structure with cartilage or bone and induce an immunologically inappropriate response against the joint
- Some bacterial cell-wall fragments coming from HS lesions may get into the bloodstream, become complexed to antibodies and then happen to deposit in synovial tissue, where they could activate complement and produce an inflammatory but sterile arthritis
- HS may expose cutaneous antigens to the immune system and thereby cause auto-immune reactions. This way, a rupture in tolerance towards antigens that may become unmasked because of the inflammatory process involved in HS is another possible mechanism.

6.4 Associated Cancers

6.4.1 Non-Skin Cancers

Growth of sinus tracts is a histological hallmark of HS. Histologically the sinus tracts often appear as pseudo-neoplastic changes, and the co-occurrence of actual cancer is therefore not only of clinical interest, but of potentially pathogenic relevance as well, and may reflect an overall trend for HS patients. To our knowledge, there is only one epidemiological study, from Sweden, addressing this matter [68]. This registry-based study concerned the relative incidence of cancer in patients treated for HS in the period from 1965 until 1997. In total 2119 patients were included. The overall risk of any cancer was increased by 50% (standardized incidence rate 95%, confidence interval 1.1–1.8) among this cohort of patients hospitalized for HS, based on the finding of 73 cases of cancer in HS patients and comparing the figure to the expected incidence in the general Swedish population. The average age at diagnosis of cancer was 51.2 years for women and 55 years for men. There was a

significantly increased relative risk not only for non-melanoma skin cancer but also for buccal cancer and primary liver cancer. Whether this increased relative risk was correlated with alcoholism and/or smoking could not be ascertained in this study. The data suggest a co-occurrence of HS and cancer but these observations await confirmation in other HS populations. If confirmed it may give direction to further aetiological and pathogenic research in HS.

6.4.2 Squamous Cell Carcinoma

Many chronic suppurative lesions such as chronic osteomyelitis and chronic leg ulcers are well known for their potential for malignant transformation into squamous cell carcinoma [69, 70]. The resultant tumours are known as Marjolin's ulcers, named after Marjolin's first description in 1826 [87]. Such tumours have been described in HS.

6.4.2.1 Incidence and Prevalence

It is very difficult to find reliable figures about the incidence or prevalence of squamous cell carcinoma in HS patients since there are very few publications describing follow-up of HS patients. Mostly isolated didactic cases are described, which increase clinical vigilance but do not provide predictive data. The risk of squamous cell carcinoma in HS has been estimated at between 1.7% and 3.2% [52]. Case reports however also allow the reader to form a clinical picture of a given problem when they are sufficiently numerous. In fact, there may be as many as 100 [87, 92] cases of squamous cell carcinoma arising from HS reported so far in the literature: these include cases arising from so-called acne conglobata of the buttocks/perineum or postsacral skin [5, 52–54, 70–93] and cases of malignant degeneration occurring in patients with "long-standing pilonidal disease, with a mean duration of 23 years" [92]. Both these diagnostic groups may potentially be confused with HS.

Reviewing the published cases there seems to be a clear predominance in men, since only eight cases of squamous cell carcinoma have been described in women [5, 53, 54, 74, 85, 88, 91, 92]. This may however partly be explained by reporting bias. For instance, vulval squamous cell carcinomas may well be under-reported in association with HS, as this diagnosis was explicitly excluded from Mora's series of squamous cell carcinoma in a black population. Predisposing factors are rarely searched for in the literature. The occurrence of non-skin cancers suggests that general carcinogens such as tobacco may play a role. Some authors have suggested that skin cancers predominate in the perineal region [52, 82], which raises the possibility of co-carcinogenic factors such as human papilloma virus (HPV) [52, 87, 88] and/or past radiotherapy [72, 88]. The presence of these factors and other known carcinogen exposure should reinforce vigilance and encourage physicians to perform a biopsy in any case of suspicious HS lesions.

6.4.2.2 Clinical Picture

The clinical picture is rather stereotypical. Lesions occur almost exclusively in the perineal area, but one case of axillary cancer in HS has been reported [94]. In almost all cases, squamous cell carcinoma arises in an individual with a long-lasting HS, usually between 10 and 30 years of duration, but extremes of 3 years [78, 92] and 50 years [85] have been reported. Lesions start insidiously with usual sinus tracts and oozing, but the recent onset of increased pain and discharge, as well as the presence of firm infiltrated subcutaneous nodules and/or extensive and ulcerated granulation tissue should alert the physician, especially if the disease has lasted for many years and keeps worsening. The tumour may rapidly enlarge and is usually resistant to any treatment including surgery except for wide excision. The diagnosis of squamous cell carcinoma is sometimes a surprise during excision for HS and discovery of an indurated area [78] or a histological surprise [88, 92], requiring a wide re-excision.

Patients may present with metastatic lymph nodes. Three cases with associated paraneoplastic hypercalcaemia have been published [75, 77, 83] and, in one of these, the presenting symp-

toms could be attributed to a paraneoplastic parathyroid-hormone-like protein [83]. Other paraneoplastic symptoms may occur and one case has been published describing a paraneoplastic neuropathy in association with HS-related squamous cell carcinoma [89].

6.4.2.3 Differential Diagnosis

Clinically, the following diagnosis may be considered: anal fistula, lymphogranuloma venereum, granuloma inguinale, Crohn's disease, tuberculosis cutis, *Nocardia* infection, actinomycosis, tularaemia, chronic pyoderma gangrenosum and erysipelas.

Biopsy should be performed to exclude malignancy. In fact, diagnosis relies on biopsy, which should be repeated in cases of suspicion, even if the first biopsy samples are reassuring, because the histological differential diagnosis with pseudoepitheliomatous hyperplasia may be very difficult [88, 91]. The clinical picture should always guide the physician; for instance, a very fast and extensive recurrence after surgery indicates a high suspicion of malignant disease.

6.4.2.4 Treatment

The only curative treatment is wide excision with re-excision if margins are too close. Surgeons insist on the necessity of assessment of margins because the tumour often spreads more widely than its external appearance would suggest [85]. Wounds heal surprisingly well in the perineal area. It has been suggested that early reconstruction may hide a recurrence, and secondary healing by granulation without colostomy has therefore been advocated [85].

Squamous cell carcinoma is a relatively chemoresistant tumour [76, 77, 85]. Radiotherapy is usually ineffective because of the extent and volume of tissue to be irradiated [72, 76, 85]. So both treatments should be considered only as palliative treatments.

6.4.2.5 Prognosis

The absence of large, well-defined cohorts precludes precise assessment of survival figures. The reported follow-up varies between 18 days and 4 years. In the early publications, diagnosis was usually very late and a rate of 50% death was seen [82]. In more recent literature this appears to have improved significantly, most likely because of the general quality improvements in health care and education. Undoubtedly the dermatological community is now more aware of this potential complication, and progress in survival rates has been made, due to earlier diagnosis and more skilled surgical interventions with wide excisions.

6.5 Other Co-Occurrences

These other co-occurrences may be pure coincidences, but they may also give us clues to a better understanding of the mechanisms of this disease. HS is occasionally seen as a side-effect to other treatments (see Table 6.4). HS has been described in several cases in association with lithium therapy, where it appears to have similarities to other poral occlusive diseases, as well as to immunosuppressive therapy used following kidney transplantation.

HS has also been described as a side-effect of rapamycin therapy, with a 12% frequency in a cohort of 80 kidney transplants. This immunosuppressive drug hints either that immune mechanisms may be involved in HS, or that simple infections may be promoted by the drug and misinterpreted as HS by non-dermatologists. The diagnostic accuracy of the reported cases however allows confusion with differential diagnosis.

Table 6.4. Drugs where hidradenitis has been implied as a side-effect

Rapamycin [95]
Lithium [96–99]

6.6 Conclusion

A number of diseases have been described as co-occurring with HS. The association may often occur by chance taking into account the prevalence of HS in the general population. The serendipitous observation of co-occurrence may however also reflect a causal relationship between the diseases, and thereby lead to a better aetiological or pathogenic understanding of both diseases. Taking all the suggested associations into account a very heterogeneous picture emerges, which does not allow hard conclusions to be made. This review of the literature strongly underlines the continued need for systematic observations in larger numbers of patients. The establishment of patient cohorts of sufficient size to allow longitudinal studies is therefore encouraged.

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Chapter 7

Hidradenitis Suppurativa and Crohn's Disease

7

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Key points

- An association between hidradenitis suppurativa (HS) and Crohn's disease (CD) appears to be well established
- Recognizing HS in a patient with CD, or vice versa, has no immediate major therapeutic implications but may lead to the choice of a more aggressive medical strategy
- One can expect that a genetic link between the two diseases will be demonstrated and may lead to the development of specific targeted therapies

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Crohn's disease (CD) is a chronic granulomatous inflammatory bowel disease that may involve the anus and the perianal region. About 50% of patients with CD develop perianal lesions during the course of their disease. In some of these patients, perianal cutaneous lesions may mimic those of HS. Moreover, the occurrence of both HS and CD in the same individual has been reported in quite a large number of cases. This paper reviews the main pathophysiological and clinical aspects of CD, describes the perianal lesions of CD, comparing them to those of HS, and discusses the links between the two diseases.

7.1 Definition and Course of Crohn's Disease

7.1.1 Pathophysiology

The cause of CD remains unknown. Recent advances in the pathogenesis of CD involve interactions of three elements: genetic factors, enteric microflora and immune-mediated tissue injury. Furthermore cigarette smoking has been described as the main risk factor for relapse and poor evolution of the disease [1].

7.1.1.1 Genetic Factors

CD appears to have a genetic tendency, with multiple susceptibility genes. The first susceptibility locus for CD, which was found in replicative studies worldwide [2, 3], is on the pericentromeric region of chromosome 16 (IBD1 locus). Mutations of the NOD2 gene in this region have been conclusively associated with CD. Homozygosity and compound heterozogosity increase the relative risk of developing CD by 20- to 40-fold compared to non-NOD2-mutated subjects. Nods proteins are thought to be cytosolic receptors for pathogenic bacterial signals. Nod2 recognizes muramyl dipeptide (MDP) [4], a conserved structure in bacterial peptidoglycan. Nod2 is expressed in monocytes and activates nuclear factor kappa B (NF-κB), which is a key transcriptional factor involved in the initiation of the inflammatory response [5]. Since NOD2 variants seem to account for less than 20% of CD, other candidate susceptibility genes need to be investigated.

7.1.1.2 Enteric Microflora

The absence of evidence for transmission of either CD or ulcerative colitis argues against a transmissible infectious etiology. However, there are several pieces of indirect evidence that commensal microflora contribute to the pathogenesis of CD, such as:

1. The failure of induction of colitis in germ-free animals [6]
2. The occurrence of inflammatory bowel disease (IBD) lesions in areas of greatest bacterial exposure
3. The induction of relapse in ileal CD by the fecal stream [7]
4. The difference of fecal and mucosal flora composition between patients with CD and healthy subjects [8]
5. The loss of tolerance to the components of endogenous flora in patients with CD [9]
6. The influence of antibiotics and probiotics in experimental animals and in some clinical situations (postoperative relapse of CD) [10].

7.1.1.3 Immune-Mediated Tissue Injury

Host–microbial interactions involve commensal species that reside permanently within the gastrointestinal tract and this adaptation actively contributes to immunological tolerance and homoeostasis within the healthy gut. Molecular mechanisms of this prokaryote/eukaryote crosstalk involve different bacterial signals and pattern recognition receptors (PPRs) such as toll-like receptors (TLRs) and NODs [11]. The bacterial stimuli represent a cluster of various signals called pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), peptidoglycans and bacterial nucleic acids (CpG DNA). TLR are key regulators of the innate immune response, and different changes in selective epithelial expression of TLRs have been reported to occur in CD [12]. In CD tissue damage arises from excessive TH1 cytokine responses or a failure to turn off such responses after pathogenic infection in genetically susceptible individuals. Additionally, cytokines act on local microvasculature, upregulate adhesion molecules and facilitate the recruitment of neutrophils and phagocytes, which contribute to the amplification of the inflammatory response and further tissue damage. In healthy individuals, activated mucosal T cells are controlled through regulatory T cells and apoptosis pathways, both of which seem to be defective in patients with CD [13].

7.2 Pathology

The elementary intestinal lesion consists of focal infiltration of mononuclear cells, eosinophils, and polymorphonuclear cells in the lamina propria, small vessels, and epithelium [7]. Lesions tend to become chronic and deeper, involving in some places all the width of the intestinal wall. Important characteristics are the

patchy distribution of the lesions, the epithelioid granulomas which are observed in up to 60% of patients, and the formation of strictures and fistulas.

7.3 Clinical Aspects

CD is usually diagnosed during the third decade of life, but is not exceptional in childhood and after 60 years.

7.3.1 Disease Location

CD may involve any part of the digestive tract, but is located most commonly to the ileum and/or the colon [14]. Most frequently, the disease location remains the same, namely ileocolonic, ileal, or colonic, throughout the course of the disease, although some patients (fewer than 10%–20%) may develop new lesions in another part of the intestine.

7.3.2 Clinical Presentation

Symptoms depend on disease location (colonic lesions being more expressive) and anatomical severity. Patients usually present with diarrhea, mucous and blood discharges, abdominal pain, and weight loss. Other features of flares are fatigue, fever, articular, cutaneous and ocular manifestations, and biological inflammatory response (elevated C-reactive protein and erythrocyte sedimentation rate, ESR). In some cases, the disease is latent until the development of a complication, a stricture causing an intestinal obstruction or a perforation (peritonitis, or more commonly internal fistula with abscess formation). The course of CD is poorly predictable. Most patients have flares separated by remission phases of variable duration; others (about 10%–15%) have a chronic active disease. The disease has a protracted benign course in fewer than 15% of patients.

7.4 Therapeutic Aspects and Prognosis

Flare-up episodes are usually treated with aminosalicylates or prednisolone, according to their clinical severity. When steroid therapy fails (10%–30% of patients), the anti-tumor necrosis factor-alpha antibody infliximab 5 mg/kg is usually active.

Maintenance treatment prescribed with the goal of preventing flare-ups uses aminosalicylates and, in more severe forms, immunosuppressive drugs (azathioprine or methotrexate). Immunosuppressants are very effective as maintenance treatment, achieving and maintaining remission, sparing steroids, leading in some cases to mucosal healing, and improving quality of life [15]. Accordingly, there is a clear tendency over time to initiate immunosuppressants earlier and in a larger proportion of patients [16]. Nowadays about two-thirds of patients receive immunosuppressants. Repeated perfusions of infliximab may be used in the few patients who are non-responders to classical immunosuppressants. Surgery is reserved for stenotic and extra-parietal complications, or intractable forms after a well-conducted medical management. The cumulative risk of intestinal surgery is 82% after 20 years.

CD is an all-life chronic disease with no tendency to burn out over time. However, most patients are able to have an almost normal life. Mortality is slightly increased when compared to the general population [17].

7.5 Cutaneous Crohn's Disease

At the time of diagnosis of intestinal CD, examination of the anus shows anal or perianal lesions in about one-quarter of patients. Later on, up to half of patients eventually develop perianal lesions. Those lesions are more frequent when CD involves the distal part of the colon and rectum, but may be associated with ileal disease without colonic involvement, and also may precede for years the development of intestinal lesions. Recent data identified a new variant gene OCTN (organic cation transporter) associated with perianal and fistulizing CD. This gene is located on the locus of IBD-5.

7.5.1 Clinical Presentation of Cutaneous Lesions

The primary lesions of CD are confined largely to the endoanal skin, the transitional epithelium of the anal canal, and the contiguous 1–2 cm of rectal mucosa. The primary lesion is a painless, midline fissure of the anal canal, which usually remains symptomless and benign. Edematous skin tags arise from the distal margin of superficial fissures. They may be voluminous, with no tendency to decrease. A second and more destructive lesion is a penetrating ulcer which gives rise to fistulas [18]. Fistulous tracts may be low, superficial, or high, long and tortuous, depending on the location of their primary opening in relation to the anal canal. They may form cavities and lead to abscess formation. They may extend to the anal sphincter and have an impact on continence. Finally, anal lesions may lead to stricture formation [19]. Over one-quarter of patients with CD will present with or develop perianal fistula.

Aggressive ulceration is an uncommon form that extends rapidly beyond the perianal skin to involve the perineum and often the vulva [18]. It is usually associated with cavitating endoanal ulcers. Involvement of skin distant to the gastrointestinal tract (metastatic CD) is uncommon, but CD affecting penile and scrotal skin has been described.

Perianal lesions should be carefully assessed and classified (ulceration, fistula, stricture) by physical examination. However examination under anesthesia and modern imaging techniques (endoanal sonography, magnetic resonance imaging) improve the detection and characterization of fistulas and abscesses, and are necessary before defining a therapeutic strategy.

7.5.2 Therapeutic Aspects and Prognosis

The overall strategy facing perianal CD is conservative [20, 21]. The control of sepsis is the first objective. Antibiotics (metronidazole, ciprofloxacin, and clofazimine) are used for self-limited complications (small abscesses, acute exacerbations without abscess formation), but not as a maintenance therapy. Surgical intervention is required for drainage of an abscess, non-cutting seton drainage of complex fistulas with deep pus collection [22, 23], and dilatation of a symptomatic anal stenosis.

The effect of immunosuppressants is not as favorable as it is on the intestinal disease. In children, purine analogs have been shown to improve perianal tenderness and induration in most patients and to achieve fistula closure in some [24]. In adults, although purine analogs may induce the closure of perianal fistulas [25], only one-third of patients with perianal lesions clearly improve. Patients aged 40 years or more, with recent perianal lesions, and without fistula are the best responders [26].

The management of perianal fistulizing disease resistant to standard treatment has greatly improved with the introduction of infliximab [27]. The complete arrest of the drainage of fistulas is obtained in 46% of patients 10 weeks after the administration of 5–10 mg/kg of infliximab at weeks 0, 2 and 6 and lasts on average for 12 weeks. However, fistula closure is often incomplete or superficial, fistulous tracts can persist despite closure of the external opening, and relapses are common. This may lead to a resumption of infliximab and to its being administered on a chronic basis (5–10 mg/kg every 2 months), with a tendency to a loss of efficacy with time. In cases of incontinence or when the lesions are severely disabling, proctectomy may become necessary (10%–38% of patients).

7.6 Crohn's Disease and Hidradenitis Suppurativa

7.6.1 Differential Diagnosis

In a patient with perianal disease, the differential diagnosis between CD and HS is usually easy, as in HS other disease sites (axillae, groin) have been involved and anal examination does not demonstrate endoanal lesions or primary ulcerations with fistula formation. Fistulas to the anal canal may occur in HS, however they do not extend more than the extreme location of the apocrine glands [28, 29]. In contrast, in CD

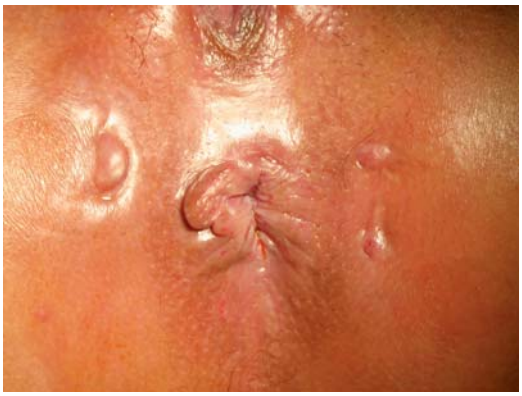

Fig. 7.1. The elementary lesions of perianal Crohn's disease (*CD*, posterior fissure, skin tags, and fistulas)

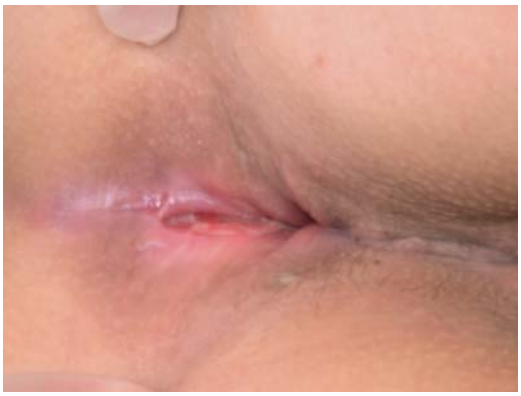

Fig. 7.2. A CD fissure merging on the perianal skin

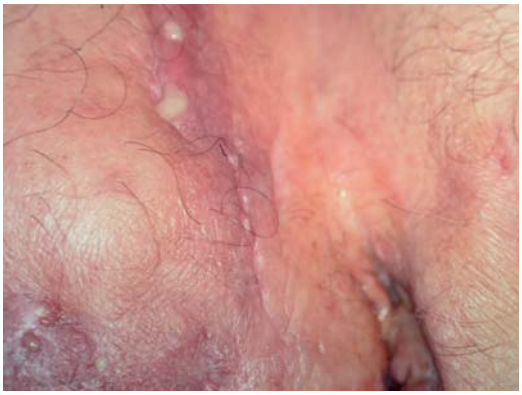

Fig. 7.3. A suppurative form of perianal CD with multiple fistulas

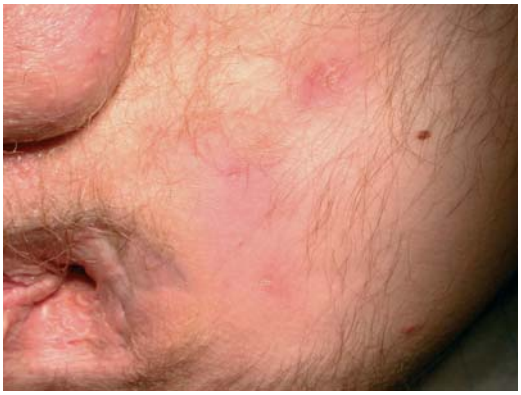

Fig. 7.4. HS lesions in a patient with operated perianal CD

anal lesions may be absent or have healed. The aspect of the perianal lesions also differs. In CD the lesions are more ulcerative, scars are retractile, and the skin is involved only around the anus (Figs. 7.1–7.3), whereas in HS, there are cutaneous scarring, comedones, skin bridges and sinuses (Figs. 7.4, 7.5). From a pathological point of view, lesions may be very similar. Attanoos et al. [30] specifically looked at the granuloma in 101 HS patients. They found that although foreign-body-type granulomas are a common feature of HS (25%), the presence of discrete epithelioid granulomas in the dermis away from the site of active inflammation is unusual and should alert one to the possibility of granulomatous disease such as CD [30].

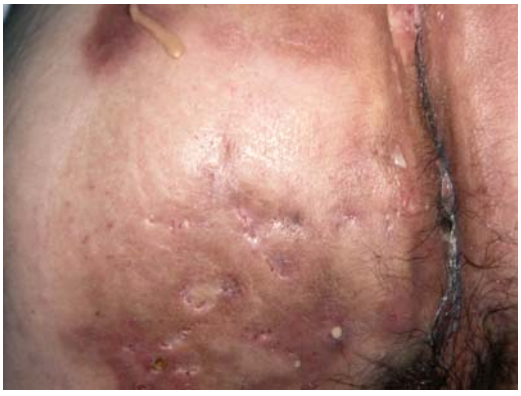

Fig. 7.5. HS lesions in a patient with CD

7.7 Co-Existence of HS and CD

A clinical association between HS and CD has been described in some cases reports [31–33] and in one case series [34]. Gower-Rousseau et al. reported the occurrence of HS in two first-degree relatives of patients with CD [35]. This finding suggests a common genetic susceptibility for the two diseases. In the study by Church et al. [34], CD lesions were found in 24 out of 61 patients with HS. In our series of 2926 patients with CD, 18 (0.6%) have such an association. This figure should be considered as minimal, as a systematic search for HS was not made. Of note, the proportion of active smokers was 78% in our patients with both diseases. Clinical characteristics of patients with HS and CD in the two latter studies are given in Table 7.1. CD patients with HS differ from other CD patients by a higher frequency of colonic and perianal involvement, an increased need for immunosuppressants, and, more importantly, a very unusual need for proctectomy and definitive ileostomy. Finally, the evolution of the two diseases is not parallel, with possible exacerbations of HS while the intestinal disease is burning out.

From a practical point of view, the occurrence of digestive symptoms or unexplained biological abnormalities (anemia, hypoferritinemia, elevated C-reactive protein) in one patient with HS should alert the physician and lead to colonoscopy, as the presence of gastrointestinal endoscopic lesions and granulomas on biopsy establishes the diagnosis of CD. Conversely, there is a need for a systematic search for acne, folliculitis, and HS skin lesions in CD patients, particularly when a steroid treatment is planned.

Table 7.1. Characteristics of Crohn's disease (*CD*) in two series of CD associated with hidradenitis suppurativa (*HS*)

	Cleveland Clinic	St. Antoine
Males/females	11/13	7/11
Median age at diagnosis of CD (years)	39 (18–75)	26 (11–50)
CD location (small bowel/colon/both)	2/20/3	3/11/4
Perianal CD	24 (100%)	16 (88%)
Excisional surgery for CD	21 (88%)	9 (50%)
Proctectomy	17 (71%)	8 (44%)
Immunosuppressants	Not indicated	13 (72%)

7.8 Treatment of Perianal Co-existent CD and HS

The use of steroids should probably be discouraged in the acute phases because of their poor efficacy and the risk of septic complications. Immunosuppressants need to be evaluated once sepsis has been completely controlled. Infliximab has been proven to be efficient in the treatment of cutaneous CD manifestations such as pyoderma gangrenosum [36]. This led some authors to use infliximab in patients with both HS and CD [37–42]. Infliximab was introduced when conventional medical treatment and surgical drainage failed. Various infliximab regimens of one to three perfusions have been reported with prolonged efficacy. Improvement was noted in both the perineal CD course and axillary or perineal HS lesions. These observations reinforce the link between the two diseases and suggest a shared inflammation pathway.

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Chapter 8

Epidemiology

8

Luigi Naldi

Key points

- Hidradenitis suppurativa (HS) is a relatively common skin disease affecting about 1% of the general population in some European countries
- Both genetic and environmental factors have been proposed for causation. In particular, smoking is a well established potentially avoidable cause
- An association with non-melanoma skin cancer needs further clarification since it may suggest common risk factors to the diseases
- HS appears to be one of the most disabling dermatological diseases, with about half of patients reporting it as a relevant problem and causing severe distress

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8.1 Introduction

The ultimate aim of epidemiologic research is to find means to prevent disease onset (primary prevention) and to restore health once a disease has been developed (secondary prevention). Additional purposes are to evaluate and optimize healthcare. It is not surprising that the main clinical areas covered by epidemiologic research are those associated with a high mortality rate in the population as a whole, such as tumors, and those involving a major disability problem, for example chronic inflammatory diseases. I believe that hidradenitis suppurativa (HS) belongs to this second group. However, the disease has been the subject of limited epidemiologic interest.

8.2 Descriptive Epidemiology

The development of effective preventive measures starts by assessing the distribution of a disease in a given population and, by comparing measures between countries, making correlations with other factors, i.e., ecological correlations. The usual measures of disease distribution are incidence and prevalence. Incidence refers to those cases newly developed in a population over a given period of time. More specifically, incidence density represents the number of new cases per person-time and is applicable to a dynamic population reflecting the speed of dissemination of the disease in the population, while cumulative incidence is the proportion of cases that develop in a fixed group over a given period of time. Such a measure reflects the probability of a member of the group developing the disease over the time considered. It should be

Table 8.1. Prevalence studies of hidradenitis suppurativa (*HS*)

Reference	Country	Sample	Assessment	Measure	Estimate
Fitzsimmons, 1984 [1]	UK	Unclear	Unclear	Unclear	1:3000
Fitzsimmons, 1985 [2]	UK	Unclear	Unclear	Unclear	1:300
Lookingbill, 1988 [3]	USA	1106 new dermatology patients	Clinical examination for hidden or unrecognized conditions	Point prevalence	1:1000
Jemec, 1988 [4]	Denmark	70 female hospital employees	Interview	Lifetime prevalence	4:100
Harrison, 1991 [5]	UK (South Wales)	Unclear	Clinical examination	Point prevalence	1:600
Jemec, 1996 [6]	Denmark	599 adults	Interview	1-year prevalence	1:100
Jemec, 1996 [6]	Denmark	507 patients at an STD clinic	Clinical examination	Point prevalence	4:100
Mahe, 1998 [7]	Mali	10,575	Clinical examination	Proportion of patients[a]	1:3000
TNS Sofres, 2005 [8]	France	6887	Interview	1-year prevalence	1:100

[a] Not a true prevalence estimate.

noted that incidence estimates require an onset for the disease to be precisely defined. For many chronic disorders characterized by prodromal signs and symptoms, such as HS, such an onset may be difficult to establish. Prevalence refers to those cases that are present in a given population, irrespective of their onset, at a point in time (point prevalence) or at any time point over a longer interval (period and lifetime prevalence). Prevalence depends on incidence and on the average duration of the disease. If a disease persists without a cure for a long time, it may give rise to significant prevalence rates even if the incidence is low. Prevalence reflects the burden of the disease in the population and it is a useful measure for planning health services.

Data concerning the descriptive epidemiology of HS are sparse and are derived from studies that adopt different methods, making comparisons difficult (Table 8.1) [1–8]. No incidence data are available, while a number of prevalence studies have been conducted. Critical issues to consider when comparing figures are: representativeness of the examined sample, the timeframe of the study, diagnostic criteria, and methods to assess cases (interview versus clinical examination). The last one is a particularly crucial issue. No validated criteria for HS are available in the published literature. The best instrument was developed in the framework of a genetic study in the UK [9]. A consensus approach, combining information from the published literature and the views of leading experts in the field of HS research, was adopted. By consensus, three key elements were required to make a diagnosis of HS: (1) typical lesions; (2) a characteristic distribution; and (3) the recurring nature over time. Based on these premise a set of typical lesions was compiled and termed "primary lesions". These were: (1) painful and/or tender erythematous papules (<1 cm in diameter); (2) painful and/or tender erythematous nodules (>1 cm in diameter); (3) painful and/or tender abscesses (i.e., inflamed, discharging papule or nodule); (4) dermal contractures (i.e., a rope-like elevation of skin); (5) double-ended comedones. The characteristic sites were chosen in accordance with the two areas most frequently affected by HS, namely axillae and groin. These areas were defined by anatomical borders and termed designated sites. To be classified as a case of HS a person must have either: (1) active

disease: one or more primary lesion(s) in a designated site plus a history of three or more discharging or painful lumps (unspecified) in designated sites since the age of 10, or (2) inactive disease: a history of five or more discharging or painful lumps (unspecified) in designated sites since the age of 10, in the absence of current primary lesions. Such a disease definition was able to detect most cases that were judged clinically to represent HS in a previous study. A possible lack of sensitivity of the definition was acknowledged. Formal validation would be necessary before its use in epidemiologic or other studies could be recommended.

The best way to assess disease frequency would be by taking a randomized representative sample of the general population. Actually, most of the available studies rely on convenient population samples based on selection procedures other than randomization. Prevalence estimates range from 3:10,000 to 4:100. These variations may be largely explained by different selection procedures and variations in the sex and age distribution of the examined samples. Interestingly, studies based on population samples are rather consistent in suggesting a 1-year prevalence of about 1%. HS is more common in females, with reported female:male ratios ranging from 2:1 to 5:1. Moreover, the age of onset may vary from childhood to middle age, with a reported average of 21–23 years [6, 9]. Recently, a French survey (TNS Sofres population survey) has provided a weighted estimate of HS 1-year prevalence based on a large representative sample of the general population [8]. The survey showed a convincingly higher prevalence of HS in females as compared to males (1.4% versus 0.6%) and a decreasing prevalence with age from 1.5% in the age group <25 years to 0.5% in the age group >55 years. The distribution of lesions may vary according to gender. In a Danish study, active genitofemoral lesions occurred significantly more often in female patients, while no sex difference was seen in the rarer axillary lesions. Non-inflamed quiescent nodules were also more prevalent in women and in genitofemoral lesions [6].

8.3 Analytic Epidemiology

The main purpose of analytic studies, including cohort and case–control studies, is to identify factors that may influence the disease frequency and to precisely estimate their contribution to disease occurrence. The results of analytic studies are best expressed in terms of relative risk. The relative risk is the ratio of the disease incidence among those exposed to a purported causal factor (risk factor), to the incidence among the unexposed. When derived from case–control studies, odds ratios provide an estimate of the relative risks.

Limited information is available on risk factors for HS. A familial history has been repeatedly documented in subsets of patients [2, 9, 10]. In a study, 14 out of 26 consecutive probands (53.8%) had a positive family history. Data from 11 families (42.3%) suggested a single gene transmission with an autosomal dominant inheritance. However, the disease frequency in the analyzed families felt short of the 50% expected of an autosomal dominant condition [2]. Among the reasons for the discrepancy, a possible hormonal influence on gene expression, polygenic rather than single gene transmission and genetic–environmental interaction may be considered.

Among non-genetic factors, smoking habits, body weight and obesity, hormonal factors, use of antiperspirants and deodorants, hair removal by a safety razor, and infections have all been considered (Table 8.2) [4, 8, 11–16]. The role of smoking was first assessed in a matched-pair case–control study in Germany [11]. Patients who had received surgical treatment for hidradenitis suppurativa in two dermatological centers were cases. As controls, patients admitted for various other skin diseases were selected and matched for sex and age to cases. Out of 84 patients treated for HS, 63 subjects (27 men, 36 women) completed the questionnaire. The rate of active cigarette smokers was 88.9% among cases and 46% in the matched-pair control group with an odds ratio of 9.4 (95% confidence interval 3.7–23.7). A proportion as high as 27% of cases reported at least one affected first-degree relative. A drawback of the study was the inclusion of prevalent rather than incident cas-

Table 8.2. Selected studies concerning potential non-genetic risk factors for HS

Reference	Country	Study design	Factor(s)	Study results
Konig, 1999 [11]	Germany	Case–control	Smoking	OR 9.4 (95% CI, 3.7–23.7).
TNS Sofres, 2005 [8]	France	Population survey	Smoking Alcohol consumption BMI and metabolic factors	Association with smoking and BMI
Jemec, 1988 [4]	Denmark	Case–control in women	Signs of androgenization	No difference except for a shorter menstrual cycle and longer duration of menstrual flow in HS cases
Barth, 1997 [12]	UK	Case–control in women	Endocrine factors	No association after matching for BMI
Morgan, 1982 [13]	UK	Case–control	Shaving and the use of chemical depilatories, deodorants, and talcum powder	No significant difference except for a more frequent application of talcum powder by controls as compared with HS cases
Jemec, 1996 [14]	Denmark	Case–control	Education, menstrual and reproductive history, oral contraceptives, BMI, earlobe piercing, use of cosmetics	HS cases better educated, younger and fewer pregnant. Pierced earlobes more frequent among HS cases
Jemec, 1996 [15]	Denmark	Case–control	STD history, current STD, STD risk factors	Genital HPV infection more common in HS patients
Lapins, 2001 [16]	Sweden	Record-linkage of hospital discharge diagnoses with the Swedish Cancer Registry	Association with cancer	SIR[a] for all cancers 1.5 (95% CI 1.1–1.8) SIR for NMSC 4.6 (95% CI 1.5–10.7) SIR for buccal cancer 5.5 (95% CI 1.8–12.9) SIR for liver cancer 10 (95% CI 2.1–29.2)

[a] SIR = standardized incidence ratio.

es, the lack of assessment of an exposure-effect gradient, and the lack of control for potential confounders on the exposure–effect relationship. However, the odds ratio was so high that confounding by unmeasured factors was unlikely. These results have been recently confirmed by data from the TNS Sofres population survey in France, where HS was strongly correlated with cigarette smoking [8]. At this time, cigarette smoking appears to be a major modifiable risk factor for HS. The effect of quitting smoking has not been assessed in HS patients who are smokers and it is worthy of consideration. In addition, the role of smoking as a prognostic factor should be evaluated. Interestingly, several case reports and a few case series point to an association between HS and Crohn's disease [17, 18]. It is well established that Crohn's disease is associated with smoking and smoking has detrimental effects on the clinical course of the disease [19].

The relationship between body weight and HS has been repeatedly considered in the lack of convincing evidence [12, 14]. Recently, the TNS Sofres population survey has rejuvenated such a proposed association by documenting a higher proportion of people who are overweight and obese among individuals reporting a history of HS with respect to the general French population (53.5% versus 44.2%) [8]. Some attention

has been repeatedly drawn toward the possible role of hormonal factors [4, 12, 14]. No convincing data are available. In a study of 66 women with HS, 23 had acne and 23 (34.8%) were significantly obese (body mass index, BMI, >30 kg/m^2). Plasma androgens were compared with controls matched for BMI and hirsuteness and no difference was documented [12]. The prevalence of HS has been found to be higher among patients attending a sexually transmitted disease (STD) clinic than in an unselected general population [6]. In principle, a selection bias may explain such a difference. However, an association with chlamydial infections has been also suggested. A case–control study based on patients in a STD clinic was unable to confirm the association with chlamydial infection [15] but, quite unexpectedly, it found a higher prevalence of genital human papilloma virus (HPV) infection among HS cases as compared with controls. The significance of such a finding is unclear and a chance effect is quite plausible. Another unexpected finding from a case–control study was the association of HS with pierced earlobes [14]. Since only univariate analysis was conducted and many confounding effects may operate (e.g., social class, age, etc.) this association should be taken cautiously.

An insight into potential risk factors for HS may come from analyses of disease associations since associated diseases may share common risk factors. In principle, associations may also result from exposures which follow the development of one of the diseases of interest (e.g., iatrogenic factors) or even represent an artifactual effect if the presence of a concomitant disease influences the diagnosis of another disease or its referral (Berkson's bias). Interestingly, in a large-scale analysis of Swedish hospital discharge diagnoses linked with data from the Swedish National Cancer Registry, a strong association was documented between HS and non-melanoma skin cancer (NMSC), buccal cancer and liver cancer [16]. These associations may at least partly reflect chance findings derived from multiple testing. However, the primary hypothesis of the study was centered on an association between HS and NMSC. Even if NMSCs complicating perineal or buttock HS localizations is a possible explanation, alternative hypotheses may involve a role for skin phenotype and/or sun exposure on the development of HS. Such a hypothesis is worthy of consideration in future studies.

8.4 Clinical Epidemiology: Natural History and Prognosis

There are limited data concerning the natural history and prognosis of HS. Ideally, a prognostic study should be based on a representative sample of affected individuals followed-up for a sufficiently long period of time. Loss to follow-up should be reduced to a minimum, outcome measures should be clearly defined at the beginning of the study, and adequate analytic methods should employed (e.g., survival analysis). A number of studies evaluating the impact of HS have been based on a retrospective assessment of patients identified from hospital records at a point in time. These studies tend to be biased toward the selection of more severe and chronic cases and may overemphasize the disability connected with HS. To standardize disease assessment over time, a stage classification would be a useful tool. A three-stage classification was proposed several years ago [20] and, more recently, a lesion, area and severity index for HS was developed [21]. The validation of these instruments would involve assessment of their repeatability, sensitivity to change and ability to predict outcome in terms of morbidity and disability over time.

All the available studies indicate that HS is a disease with a remarkable impact on the patient's life. An analysis of American hospitalization records shows that more patients with HS receive a principal diagnosis – the chief reason for the hospital stay – than those with psoriasis. This indicates that HS has a much higher morbidity than other dermatoses such as psoriasis [22, 23]. In Denmark, the general self-reported level of health is poorer among HS patients. Due to flare-ups, an average 2.7 days of work per year is lost by Danish patients (stages I and II) [14]. The soreness, discharge, and appearance of lesions are described as problems in both work and leisure activities by 51% of all patients. For grades I and II, the main problem was soreness,

which can be used to assess the efficacy of treatment [22, 23]. In the context of the TNS Sofres survey, which is deemed to provide a representative sample of patients with HS in France, 47.2% of HS patients reported a medical consultation for their disease in the year preceding the interview, and 47.7% of the patients reported HS to be a relevant problem and a severe distress [8]. In a survey of the Dermatology Life Quality Index (DLQI) in 114 HS patients, the mean DLQI score was 8.9 (SD ±8.3) points. The highest mean score out of the 10 DLQI questions was recorded for question 1, which measures the level of pain, soreness, stinging or itching (mean 1.55 points, median 2 points). Patients experienced a mean of 5.1 lesions per month [24]. In a questionnaire-based survey among HS patients identified from hospital records of three hospitals in Nottinghamshire (UK) 110 HS patients were interviewed. The average reported age of disease onset was 21.8 years. At the time of the survey patients had suffered on average disease duration of 18.8 years. Most patients (98 of 110) still had experienced active disease within the past year. In women the condition had a tendency to ease or subside after the menopause. Forty-four per cent of women felt that their condition was aggravated by menstruation. The average duration of painful boils was 6.9 days. In addition, 62% of patients acknowledged the presence of permanently painful boils that failed to subside. Patients developed a median of two boils per month. Factors that could aggravate the condition were primarily sweating or heat, stress or fatigue and tight clothing or friction. Factors that could improve the condition consisted largely of a variety of medical treatments and a number of lifestyle measures, such as swimming or baths. Twenty-four per cent of patients had failed to find anything at all to help their condition, despite an average disease duration of almost 19 years. HS appears to be one of the most distressing dermatological diseases [25].

A few case reports exist describing rare but serious complications. Complications of long-standing untreated disease include amyloidosis, leading to fistula formation into the urethra, bladder, rectum, or peritoneum, lymphatic obstruction and lymphoedema of the limbs, scrotal elephantiasis [26]. Chronic HS-associated arthritis, axial spondyloarthropathy, and sterile osteomyelitis-like lesions also occur [27]. Squamous cell carcinomas originating from HS lesions may complicate perineal and buttock localizations.

8.5 Perspectives

HS is a relatively common skin disease affecting about 1% of the general population. Both genetic and environmental factors have been identified as potential causative factors but assessment of their importance is hampered by the lack of systematic analyses considering potential confounding effects and interactions. For the future a larger collaborative research network promoting more systematic research activity would be desirable. Relatively simple measures, such as prevalence rates, are of great interest if obtained according to uniform methods in different countries, e.g., several European countries, allowing international comparison and ecological correlations. The development of HS is likely due to the effect of concurrent etiologic factors, which should be better assessed in a simultaneous way. Family history and smoking habits are well established causes. They should be considered in any future etiologic study including genetic studies where a genetics–environmental interaction may play a role. An area in urgent need of attention is clinical epidemiology. Perhaps the best way to analyze outcomes and associated factors (i.e., etiologic and predicting factors) is through long-term cohort studies of representative samples of newly diagnosed HS patients. In the context of a cohort, risk factors for disease relapse or other "sentinel" events, e.g., cancer development, could be efficiently evaluated by nested case–control studies or case–cohort analyses. Finally, large-scale pragmatic randomized trials would be the best way to evaluate the impact of complex or non-pharmacological interventions (e.g., lifestyle changes) on disease progression.

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Chapter 9

Nosology and Classification

9

Jean Revuz, Gregor B.E. Jemec and James Leyden

Key points

- Classification should be based on explicit criteria, e.g., etiology, pathogenesis or even therapy
- The current understanding of HS identifies it as a unique disease, clearly different from acne or folliculitis for example
- A better future understanding of the etiology and pathogenesis may resolve HS's current nosological impasse

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9.1 Introduction

Dermatologists are clever classifiers. We master a repertoire of approximately 2000 different diagnoses, which can be classified and structured. Classification of diseases is very important. By classifying biological phenomena, we structure our understanding of the underlying biological complexity, and thereby make it possible for us not only to ask meaningful positivist scientific questions, but also offer help to our patients.

Two threats exist in all classification systems, splitting and lumping, and both are equally serious. Splitting occurs when the same disease entity is split into numerous diagnoses depending on, for example, location, a good example being pityriasis amientacea and scalp psoriasis. This overwhelms the reader with diagnoses that are not essentially different, but that have been classified as different because of an essentially random aspect of the disease, e.g., location or clinical appearance. This does not allow a meaningful use of existing knowledge by direct transfer, and therefore erodes the understanding of the underlying pathogenic process as well as accumulation of clinically relevant knowledge.

The other extreme is lumping, where all diseases are lumped together pell-mell in large categories, where little consideration is given to significant etiological, pathogenic, and clinical differences between disease entities. It may be speculated that several of the more common dermatological diseases fall into this trap, as clinical experience suggests significant inter-individual differences in regard to treatment response or prognosis.

Nosology should be based on defined parameters, e.g., anatomy (gross and microscopic), etiology, pathogenesis or therapy. It should provide clinically meaningful distinctions between disease entities in order not only to promote the understanding of the disease and accumulation of knowledge, but also to help practical management.

9.2 Morphology

9.2.1 Anatomy

Hidradenitis suppurativa (HS) was originally classified according to location, and this remains a hallmark of the disease. Shortly after the diagnosis was established, an erroneous association with apocrine glands was made and the name created. A classification according to topography alone obviously does not improve the understanding of pathogenesis and hence is of little help. The erroneous classification according to an incorrect deduction based only on simple co-localization obviously delayed the development of knowledge This mistake comes from a paradox: the lesions of HS are predominantly or exclusively situated in the regions of apocrine sweat glands, yet the histological picture is one of follicular obstruction like that seen in acne lesions, and sweat gland involvement is usually absent from early lesions. The apocrine sweat gland's excretory canal opens into the follicular duct immediately above the sebaceous duct (see Fig. 9.1). This distinctive anatomical characteristic may explain the repercussions of follicular obstruction, with retention and subsequent infection and inflammation in the apocrine sweat gland. Follicular abnormalities may be a key factor of HS: they are apparent in histological as well as ultrasonographic studies of hair follicles in HS patients (see Chaps. 4, 5). There is also clinical evidence suggesting a relationship between HS and an anatomical anomaly of the pilosebaceous duct in the high prevalence of pilonidal cysts in HS patients. In one series (Faye O, Bastuji-garin S, Poli F, Revuz J. Hidradenitis suppurativa: a clinical study of 164 patients; manuscript in preparation) 30% of 164 patients are reported to have co-existing pilonidal sinus ducts.

HS is clearly a follicular disease located to restricted areas of the body. The pathogenic process in the hair follicle may be elucidated from histology, and appears to be rupture of the deeper parts of the follicle, with spillage of the follicular contents into the dermis and subsequent inflammation (see Chap. 4). The exact cause of the rupture is however not established. So even if HS can be classified as a folliculitis, just as acne vulgaris, this classification does not aid our understanding significantly, and additional aspects of the diseases must therefore be considered.

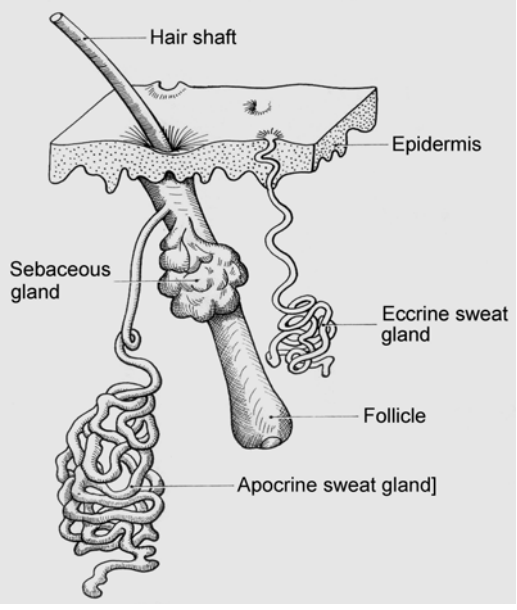

Fig. 9.1. The anatomy of the hair follicle

9.2.2 Clinical Features

The clinical characteristics of HS, i.e., deep-seated lesions and topography, are very specific and the hallmark of the disease; however, they are not explained by the histological pictures which form the main evidence for establishing a connection with acne and the so-called follicular obstruction diseases. Exceptional case reports of an association of HS with dissecting folliculitis of the scalp, acne conglobata, large epithelial cysts and pilonidal cysts have focused attention on a possible common mechanism shared by these diseases and their grouping together under the term "follicular obstruction diseases." Some case reports of an association with Dowling–Degos pigmentation of the flexure also point to a follicular obstruction. In spite of these anecdotal reports, the prevalence of acne in HS patients is identical to the prevalence in controls. The rarity of these reports and the

Table 9.1. Similarities and differences between acne vulgaris, acne conglobata, hidradenitis suppurativa (*HS*), and folliculitis. Etiology reflects known mechanisms such as inflection in simple folliculitis, morphology describes similarities in clinical morphology, pathogenesis describes similarities in known pathogenesis, e.g., seborrhea, and treatment describes response to similar treatments, e.g., response to isotretinoin

Similarities between follicular diseases			
Acne conglobata	Acne vulgaris Etiology – ? Morphology – no Pathogenesis – ? Treatment – yes	Acne conglobata	HS
HS	Etiology – no Morphology – no Pathogenesis – no Treatment – ?	Etiology – ? Morphology – ? Pathogenesis – ? Treatment – ?	
Folliculitis	Etiology – no Morphology – no Pathogenesis – no Treatment – yes	Etiology – no Morphology – yes Pathogenesis – no Treatment – yes	Etiology – no Morphology – yes Pathogenesis – no Treatment – yes

potential for positive reporting bias therefore raise questions about the validity of this assumption.

As for individual lesions the differences between acne and HS are significant: the deep-seated nodules and the absence of closed comedones – hallmark of acne – are characteristics of HS. Open comedones – black heads – are regularly observed in old lesions of HS, frequently as double or multiple comedones, but these are secondary lesions, i.e., tombstone comedos. Scarring is also more prominent in HS than in acne. In particular, the hypertrophic cicatrizing process, which leads to the formation of highly specific rope-like scars, is another characteristic of HS, very rarely seen in acne. Finally the timespan of the diseases differ. The long-lasting evolution of HS over decades is in sharp contrast with the usually self-healing nature of acne. The reclassification of the disease as acne inversa does not adequately reflect the unique features of HS and carries a serious risk of drawing incorrect analogies to acne.

Looking at four key factors of clinical relevance which may be used for classification of diseases (etiology, morphology, pathogenesis, and treatment) a comparison between acne vulgaris, acne conglobata, HS and folliculitis is made in Table 9.1. As can be seen from this, all these diseases have similarities and differences, which can reasonably be said to influence their classification.

9.3 Etiology; Pathogenesis

The etiology of HS is not known.

9.3.1 Infection

There are no convincing data to suggest that HS is primarily an infectious disease (see Chap. 11). The polymicrobial infection (or colonization) of HS – *Staphylococcus aureus*, Gram-negative rods, anaerobic bacteria – is quite different from the usual colonization of acne by *Propionibacterium acnes* and coagulase-negative staphylococci. The role of bacteria in HS may therefore be either secondary to some as yet unknown mechanism, or purely secondary once anatomical disruptions are established. HS is not a primary infectious disease; yet the initial inflammatory changes can be produced by a bacterial colonization of the follicular area similar to the triggering event of acne. The amount of inflamma-

tion and related pain is however quite different from what is observed in acne, even in the nodular variety. This may be due to the localization of the lesions but may also point to either a specific non-infectious inflammatory phenomenon, or a sequential series of events in which bacterial involvement occurs at specific points. Early involvement of pathogenic bacteria may be responsible for establishing inflammation, which leads to destructive scarring and extension of the disease independently of bacteria. Eventual secondary bacterial superinfections would then maintain the inflammatory process without the need for permanent colonization with pathogenic bacteria. The dramatic improvement observed in some patients with severe HS following a 3-month course of clindamycin–rifampicin treatment suggests a role for infection in advanced disease (see Chap. 15). However, it does not rule out the possibility that this polymicrobial infection is only a secondary phenomenon, or that these antibiotics exert a predominantly anti-inflammatory effect. A specific anti-inflammatory role of some antibiotics – including tetracyclines, clindamycin and rifampicin – has been demonstrated in in vitro experiments. Whether this action is relevant in vivo and independent from any anti-infectious activity remains to be established.

9.3.2 Inflammation

The exact cause of the rupture of the follicle is not established, although a lymphocytic inflammatory infiltrate appears to be present in early lesions (see Chap. 4). There is some evidence of infundibular epithelial hyperproliferation as well. In older lesions, sinus tract formation predominates the histopathology. It is speculated that the introduction of follicular material into the dermis as well as secondary colonization of sinus tracts cause flares of HS. These mechanisms suggest that HS can be classified as a folliculitis of unknown origin affecting the deeper end of the hair follicle and not involving the sebaceous glands. The polymicrobial colonization of HS, the efficacy of anti-inflammatory drugs, of anti-tumor necrosis factor (TNF) drugs, and the significant association with Crohn's disease all point to an abnormality of immune and/or inflammatory mechanisms in HS. The number of "candidates" is large, including abnormalities of innate immunity, e.g., NOD, TLR, and deficiencies of natural antibacterial substances such as defensins and cathelicidins (see Chaps. 6, 12). The potential usefulness of anti-inflammatory and immunosuppressive therapy in HS may therefore have a broader scope than is reflected in existing literature.

9.3.3 Hormones

The absence of any significant hormonal abnormality (see Chap. 12) and above all the normal sebum excretion rate in HS areas as well as in seborrhea-prone areas clearly put HS apart from the acne spectrum.

9.3.4 Treatments

Classification can also be made along purely practical lines, i.e., from the therapy. To classify diseases according to their response to standardized therapies may appear non-academic but is useful in practice and allows more specific speculations to be made about the etiology and pathogenesis when the therapeutic principle of the drug is known. In HS, clindamycin–rifampicin, anti-TNF biologics, sometimes corticosteroids and even immunosuppressive drugs may be helpful, while they are not useful in acne. In contrast, the retinoids, which are the most effective drugs in the treatment of acne, appear generally ineffective in HS (see Chap. 17). Thus the terminology acne inversa may lead to an erroneous management. The lack of efficiency of retinoids is in good agreement with the absence of local seborrhea and supports the classification of HS as a follicular disease different from the acnes.

9.4 Conclusion

HS is multifactorial. Follicular occlusion and disruption are predisposing factors, but other factors, including bacterial colonization and an as yet unknown pro-inflammatory mechanism, are at work. HS can be described as inverse recurrent suppuration according to topography, clinical evolution, and morphology. Looking at the parameters of etiology, morphology, pathogenesis, and therapy, HS can be differentiated from the acnes and from simple folliculitis.

Chapter 10

Genetics of Hidradenitis Suppurativa

10

Jan von der Werth, Pam Wood, Alan D. Irvine, W.H. Irwin McLean

Key points

- The genetics of HS has received little attention so far
- A familial form of HS affects up to 40% of sufferers
- Familial HS follows an autosomal dominant inheritance pattern
- A study of the molecular genetics of HS has found linkage to two loci on chromosomes 6 and 19 in three families but no linkage to either of these loci in other families
- HS is a genetically heterogeneous disease with mutations in genes at multiple locations

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10.1 Clinical Genetics of Hidradenitis Suppurativa

Like many other aspects of hidradenitis suppurativa (HS), its heritability has received little attention for many years. References to it were made by Brunsting in 1952 in his description of the follicular occlusion triad – acne conglobata, dissecting cellulitis of the scalp, and hidradenitis suppurativa [10]. As late as 1968 Knaysi reported rather dismissively that only 3 out of 18 questioned patients had described a positive family history of the disease [36]. A case report of familial occurrence of HS in association with acne conglobata was published by Gold and Delaney in 1974 [22]. A structured investigation of the genetic basis of HS was not carried out until Fitzsimmons et al. published their series of HS families in 1984 and expanded this in 1985. In these studies an autosomal dominant pattern of inheritance was postulated for a proposed

familial variant of HS [18–20]. Fitzsimmons' research analysed 23 families of probands with HS and found evidence in favour of a single-gene Mendelian inheritance in 11 of these. Their study acknowledged lacking conclusive proof of such heritability and the existence of some inconsistencies. They only ascertained the disease in 34% of first-degree relatives of HS sufferers and found a predominance of females in their group of HS sufferers by a ratio of 2:1. They also struggled to explain the marked heterogeneity of the recorded pedigrees. Assuming incomplete ascertainment, variable disease penetrance and negative recall and reporting biases from some patients, they nonetheless felt that HS was likely to be a dominantly inherited single-gene disorder. Cautiously, though, they recommended a periodic re-examination of the investigated families [18–20].

Such a re-examination was carried out in 1998, when von der Werth et al. proposed a detailed disease definition for HS and used this as a base for a review of the Fitzsimmons families 15 years after the initial study [61]. The definition used for the purpose of this study was:

"To be classified as a case of hidradenitis suppurativa a person must have either:

Active disease: 1 or more primary lesion(s) in a designated site plus a history of 3 or more discharging or painful lumps (unspecified) in designated sites since the age of 10

or

Inactive disease: a history of 5 or more discharging or painful lumps (unspecified) in designated sites since the age of 10 in the absence of current primary lesions."

"Primary lesions" had been defined as:

1. Painful and /or tender erythematous papules (<1 cm in diameter)
2. Painful and/or tender erythematous nodules (>1 cm in diameter)
3. Painful and/or tender abscesses (= inflamed, discharging papule or nodule)
4. Painful and/or tender dermal contractures (= rope-like elevation of skin)
5. Double-ended comedones.

"Designated sites" were chosen in accordance with the two areas most frequently affected by HS, namely axillae and groin.

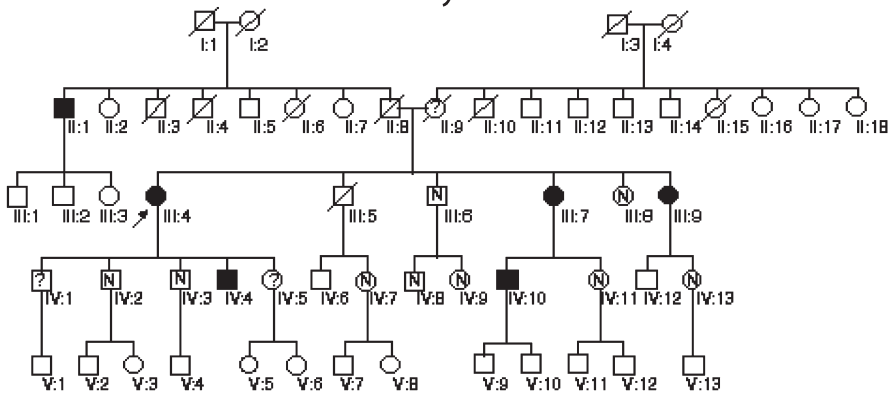
They reviewed 14 surviving probands and their families. Seven of these probands had previously been noted to have a positive family history whereas the others had been classified as having a negative or possible family history (Fig. 10.1 a, b). In all, 132 family members were assessed for their respective disease status. Participants were initially contacted by telephone or letter, and those who acknowledged a history of at least one previous boil were invited for a personal examination and interview. Only personally examined individuals could be classified as a case.

In total, 28 relatives with HS were detected, and 27 of these were in the group previously labelled family history positive. Nine of these cases had not been detected in the previous study and in at least seven of these the disease had developed after the previous study had been conducted. Only twice did their disease criteria fail to confirm cases that had been labelled as HS in the previous study. Both times they classified the patients as "possibly affected". A further 16 relatives were judged to be possibly affected. In the group with positive family history they found 10 affected and 9 possibly affected individuals amongst 37 surviving first-degree relatives of HS sufferers [61].

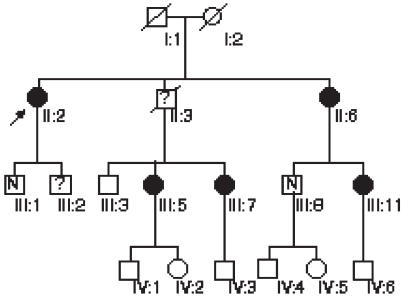
The findings in this study supported the concept of a familial form of HS with autosomal dominant inheritance. An insufficiently sensitive disease definition, a variable degree of gene penetrance and possibly a hormonal influence on gene expression were considered as explanations for the reduced risk to first-degree relatives, which falls short of the expected Mendelian value of 50%. The study was felt to be sufficiently convincing to commence the search for the proposed molecular defect behind this condition [61].

Group A
(Family-history positive in previous study)

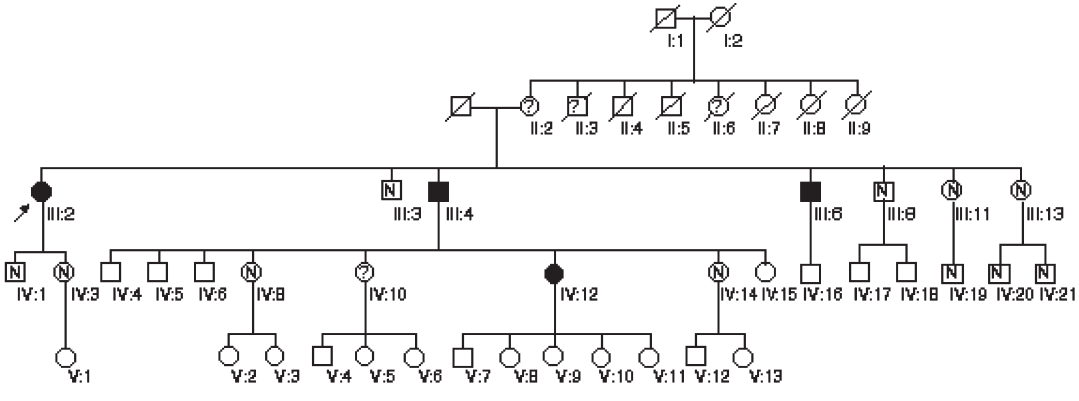
Family 13



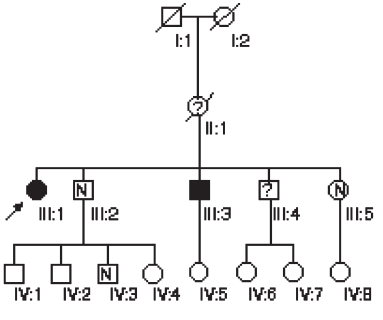
Family 15



Family 17



Family 2



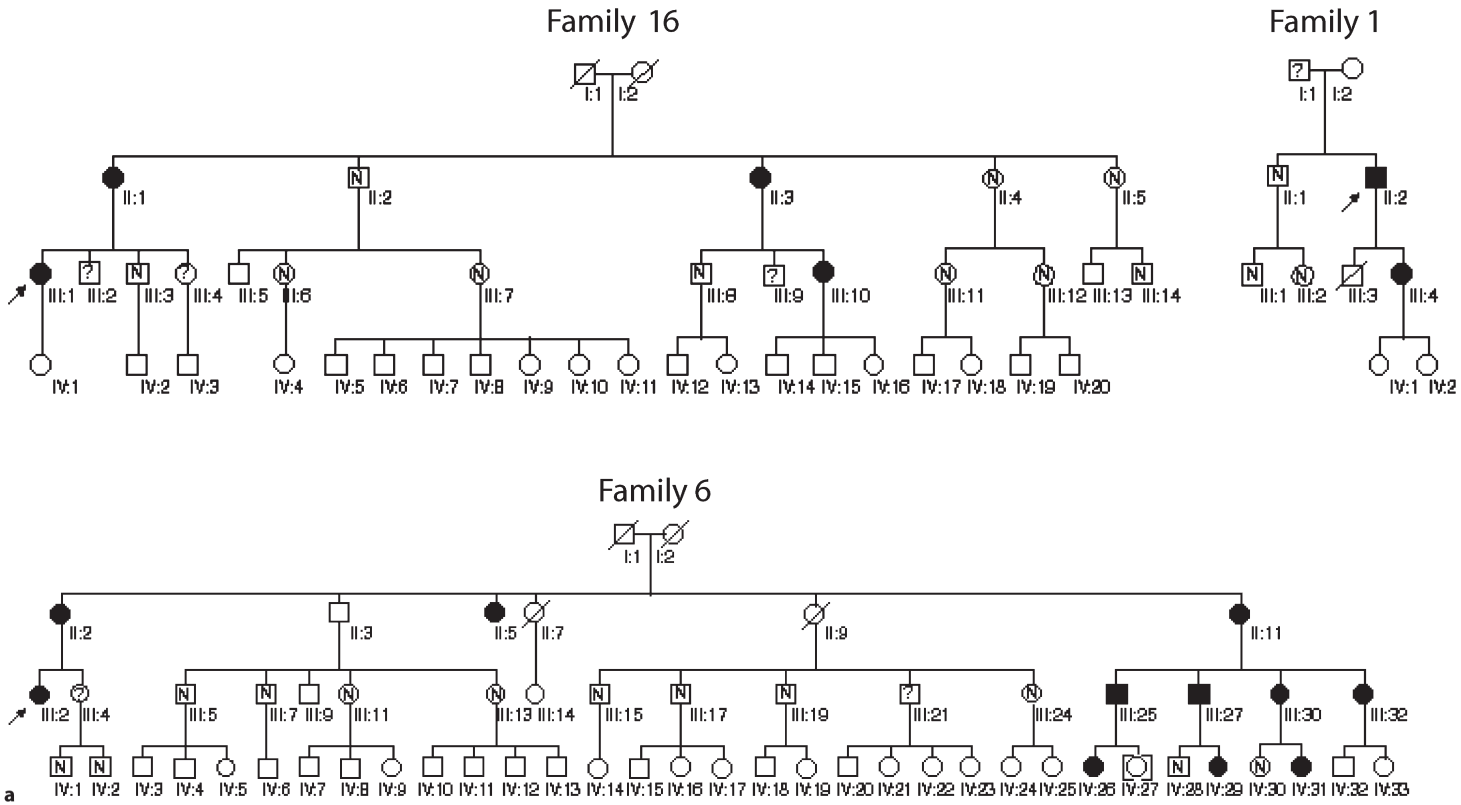


Fig. 10.1a, b. **a** Pedigrees of families with previously identified positive family history. **b** see next page

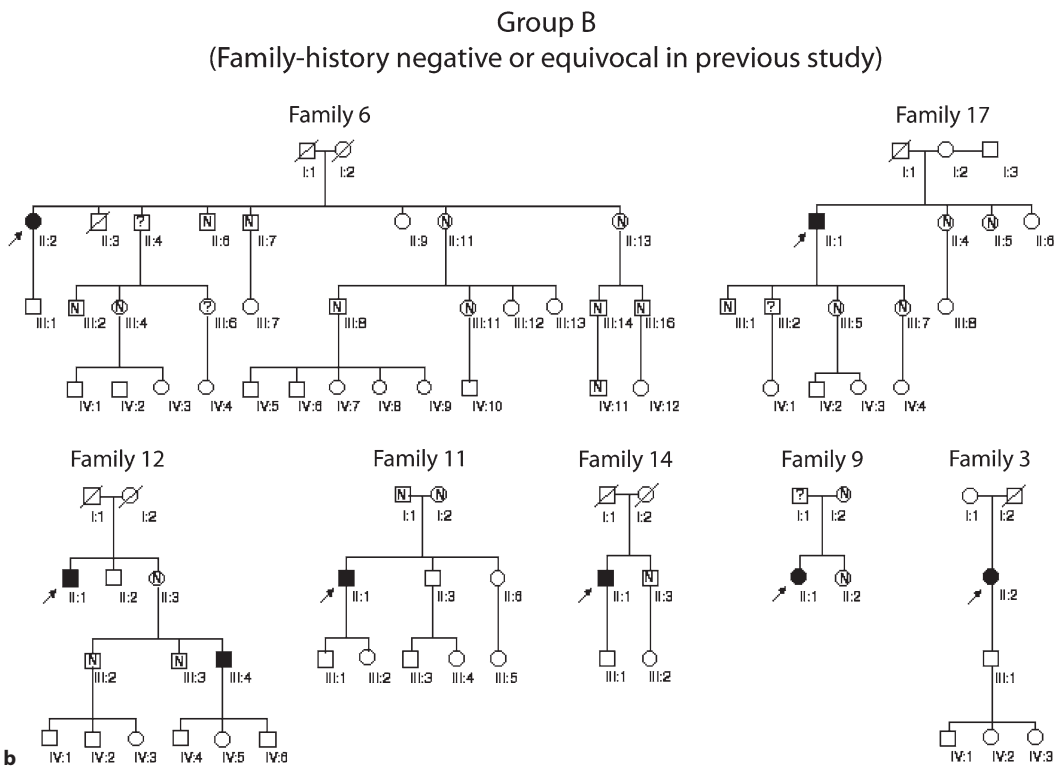


Fig. 10.1a, b. **b** Pedigrees of families without evidence of family history in prevoius study

10.2 Genodermatoses

The genetic basis of many common genodermatoses has now been identified. By 2003 over 350 single-gene skin disorders had been characterized at a molecular level [41]. These represent only a fraction of the well over 1000 single-gene disorders now known [1]. The X-linked Duchenne muscular dystrophy locus was the first disease to be mapped. It was mapped to Xp21 in 1982 but it took several years for the gene to be cloned [65]. The first gene causing an inherited skin disease was discovered in 1987 and was identified as the steroid sulphatase gene underlying recessive X-linked ichthyosis [7]. The completion of the human genome project has been a further major milestone on the road to unravelling the secrets of our genetic code. It has led to the creation of new genomic and proteomic databases which, combined with newer technology such as the development of DNA microarrays, may soon allow radical new insights into the pathogenesis of known diseases.

10.3 Methods for Identifying Disease Genes

A project to fully determine the nucleotide sequence of the human genome was formally proposed in 1985 and the human genome-mapping project was initiated in 1990 [13]. The human genome-mapping project did not, however, begin until 1998. The biotechnology company, Celera, reported the first assembly as early as June 2000 and the publicly funded effort by October 2000. The near completion of the human genome-mapping project has greatly facilitated the identification of the genetic basis underlying a vast range of dominant and recessive diseases.

There is about 2.9 Gbp of genomic sequence in the human genome, containing information for all proteins, regulatory elements and structural elements. The number of genes within the human genome was predicted to reach around 140,000 but sequencing of the human genome and analysis of its structure and sequence have lowered the predicted number of human genes to about 25,000, although these probably encode many more proteins due to alternate splicing [13].

There are several ways in which to identify and isolate the gene underlying the molecular basis of an inherited disease. The three main techniques for achieving this are: (1) functional cloning/candidate gene approach, when there is a protein of known function missing or abnormally expressed in the patient and the nucleotide sequence of the gene is obtained through the protein in question; (2) positional cloning, which identifies a disease gene based on its approximate chromosomal location; and the (3) positional/candidate gene approach where previously isolated and cloned genes are screened with a possible link to the disease based on their function or expression pattern [4].

10.4 Genetic Markers

The mapping of human disease genes requires genetic markers. Any polymorphic Mendelian character can, potentially, be used as a marker to map a disease gene. DNA polymorphisms within the human genome have provided sets of markers sufficient in number and density that have been mapped to a specific chromosomal location. Complete genetic maps allow gene localization resulting in genetic diagnosis. The first generation of DNA markers was based on restriction fragment length polymorphisms (RFLP) that were typed by Southern blotting from restriction digests of the test DNA and hybridized to radiolabelled probes. The disadvantage of this type of mapping was the presence of only two alleles, the site is either present or absent and so is not very informative. Donis-Keller et al. published the first comprehensive human genetic map in 1987 based on 403 polymorphic loci, 393 of which were RFLP markers [16]. The average resolution of the markers was about 10 centiMorgans (cM) and, as previously mentioned, they were not very informative. The development of the polymerase chain reaction (PCR) has greatly facilitated genetic mapping by allowing amplification of the marker region and analysis on automated gel analysers, and more recently capillary electrophoresis [43]. Now markers are more commonly labelled with a fluorescent dye, amplified by PCR and analysed on an automated system.

The most popular polymorphisms used presently for physical mapping are microsatellites. The discovery of the highly polymorphic microsatellite sequences within the genome has allowed the construction of genome-wide linkage maps with a high resolution [51, 63]. Microsatellites are abundant, dispersed throughout the genome, highly informative and easy to type by PCR. Analysis on automated systems then allows the genotypes to be read directly as sizes of alleles in base pairs. Human genetic mapping has focused on the construction of high-resolution linkage maps and the human genome now contains thousands of markers covering the entire genome with a density of less than 1 cM [58].

10.5 Positional Cloning of Dominantly Inherited Disease Genes

Positional cloning utilizes linkage maps and physical maps, containing information about the position of polymorphic markers to identify the approximate chromosomal location of a disease gene. The initial step is the identification of a chromosomal region that is transmitted within a family along with the disease phenotype of interest. Linkage analysis depends on informative meioses within families and heterozygosity of the markers. An individual will inherit a pair of alleles from the same chromosomal segment from each parent. Alleles on the same chromosomal segment will tend to be transmitted as a block throughout a family [52]. Families typed with a series of nearby polymorphic markers can be assigned a haplotype that is visualized as allele sizes for each marker. The heterozygosity

of a marker depends on the frequency of heterozygotes in the population at that locus. Markers with a high frequency of heterozygotes are the most informative and allow distinction between the maternal and paternal alleles. The further apart two markers are, the greater the likelihood of a recombination event occurring during meiosis. Recombination can be calculated within a family as the recombination fraction (RF). This is calculated as the number of recombinants for a given marker divided by the total number of possible recombinants. Therefore, the proportion of offspring who are recombinant is known as the RF between two loci [52]. Genetic distance, measured in centiMorgans (cM), is based on the recombination rate between two homologous chromosomes during meiosis. The recombination rate or RF is generally greater in females than males but, on average, 1 cM corresponds to 1% recombination. In many regions of the genome, this equates to approximately 1 Mbp of DNA.

Once the disease phenotype appears to cosegregate with a certain marker allele, it is possible to calculate the probability of these two loci being linked. The RF value allows evaluation of the likelihood of a pedigree for linkage based on assumptions that the loci (disease gene and marker) are either linked (RF = 0) or not linked (RF = 0.5) [54]. It is possible to compare the probability of obtaining the offspring observed if the two loci being considered are linked at a defined recombination fraction with the probability of obtaining these offspring if the loci are unlinked (RF = 0.5). The logarithm of this ratio is known as the LOD score. Positive LOD scores point towards linkage of a disease gene with a marker whereas a negative LOD score indicates the two loci are not linked [54]. LOD scores of –2 or less are obtained when the odds against linkage are 100:1 and this value is accepted as indicating that two loci are not linked. A LOD score of 3 or above is the threshold for accepted linkage, which corresponds to 1000:1 odds that the loci are indeed linked [51]. Values between –2 and 3 are, on the whole, inconclusive. Only recombination fractions between 0 and 0.5 are informative and the most likely RF for a given pedigree is the one at which the LOD score is highest. In general each informative linked meiosis in a dominant pedigree will contribute 0.3 to the LOD score, therefore a family of at least 11 members is required to produce significant linkage. Offspring of unaffected individuals in a family with an autosomal dominant disease will not contribute to the LOD score. Difficulties in linkage analysis are encountered with heterogeneity of disease locus, misdiagnosis and reduced penetrance. The penetrance is irrelevant for affected individuals but for unaffected individuals they have to be scored as possibly affected or unknown. This is due to the fact that they may be carrying the disease allele but will not show any physical symptoms. Where there is possible misdiagnosis, complexity in the inheritance or heterogeneity of phenotype, mapping using only definitely affected members circumvents this problem.

Positional cloning gives the approximate chromosomal location of a disease gene, but these regions are usually large, often several megabases in length. Once a candidate region has been identified, the standard procedure is to use higher density markers to narrow down the region. This relies on informative meioses occurring within families and may still leave the candidate locus as a large region. Linkage disequilibrium (LD) has been successfully used for fine mapping of the candidate region. LD refers to the non-independence of alleles at different sites. Single nucleotide polymorphisms (SNPs) can be used to fine map the candidate region as they are more abundant and more concentrated than microsatellite markers. Inheritance of each SNP can be used to assess for co-segregation with the disease phenotype and for SNP changes specific to a disease phenotype [8].

Once a candidate gene has been identified, the genes in this region undergo mutational analysis, usually by PCR and direct sequencing. Candidate genes can be identified in the region due to their function or expression and screened first. PCR using genomic DNA will identify any missense, splice site, frameshift or nonsense mutations within the region of the gene amplified by primers. It may not, however, identify larger genomic deletions, intronic mutations that affect splice sites or promoter mutations if the primers are not designed to specifically screen for these. In order to identify these types

of mutations it is often beneficial to screen cDNA, reverse transcribed from mRNA. This type of analysis can, in combination with exonic polymorphism, indicate if both alleles are being expressed or if one has been downregulated. It can also demonstrate any aberrantly spliced transcripts.

10.6 Genome-Wide Linkage Analysis in Familial HS

Genome-wide linkage analysis has been performed on a number of families with autosomal dominant HS. Two regions on two different chromosomes co-segregated with the disease and the genes within these regions have been analysed [64]. Although no mutation has been found some of the genes appeared to be good candidates due to their function or expression.

Three families (designated Family 6, Family 13 and Family M), which showed autosomal dominant inheritance of HS, were used to perform genome-wide linkage analysis looking for co-segregation of the disease with a number of markers. Individuals were assigned as either affected or unaffected based on their ability to fulfil certain strict diagnostic criteria as outlined above. A number of smaller families were used to check for linkage with the regions found.

Families 6 and 13 (Figs. 10.2, 10.3) were examined by one of us (JvdW) [61]. These two families were also part of the original HS study by Fitzsimmons et al. [19]. Classification of each member of the families as affected or unaffected depended on three key elements: (1) typical lesions; (2) characteristic distribution; (3) recurring nature of the lesions, as described above. Using these criteria, 12 individuals were classi-

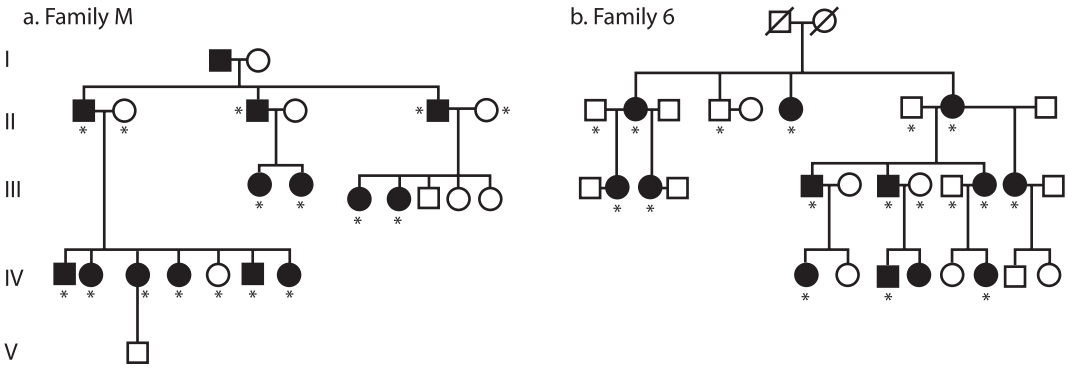


Fig. 10.2. Pedigrees of HS families studied (Families M and 6). *Asterisks* indicate the individuals used in the study

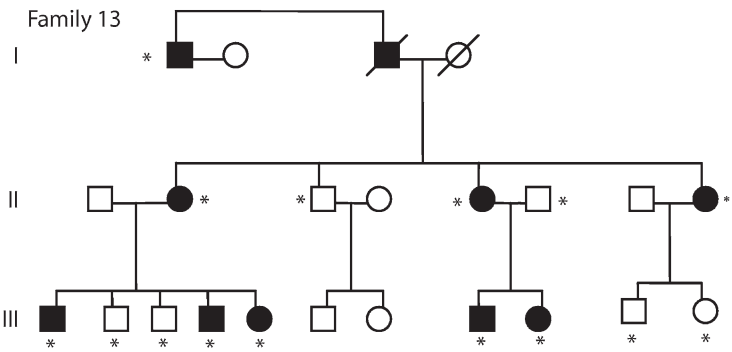


Fig. 10.3. Pedigree third family studied (Family 13). *Asterisk* indicates individual whose DNA was used in study

fied as being affected in Family 6 and 8 affected in Family 13.

A third family, Family M (Fig. 10.3), was examined by two of us (JvdW and ADI). Blood samples were obtained from 16 individuals, 12 of whom were classified as affected and 3 as unaffected according to the criteria discussed above. Pilonidal cysts and inguinal folliculitis are associated features of HS and any individuals in these families with these clinical features were also assigned as affected. Any individuals that were designated only as possibly affected were excluded from the study.

Genomic DNA was isolated from whole blood. Genotypes of affected and unaffected family members were generated initially using a set of 400 fluorescently labelled microsatellite markers. These were PCR amplified and the resultant PCR products were analysed on an automated genetic analysers. Allele sizes were determined using Genotyper 2.0 software.

ABI Prism Linkage Mapping Set-HD5 was used in regions that were non-informative. Genetic analysis was performed using higher density markers spanning candidate regions in order to reduce the size of the locus. Additional markers were obtained from data in the Human Genome Browser Database, April 2003 freeze (http://www.genome.ucsc.edu). They were amplified and analysed as described above. Two-point LOD scores were obtained using the CYRILLIC 2.1 package in conjunction with the MLINK program, assuming 90% penetrance of the disease.

All genes in the chromosome 6 candidate region were analysed. A candidate gene approach was undertaken with the chromosome 19 locus.

PCR fragments that contained a deletion or insertion and could not be sequenced were cloned into a plasmid vector, pCR2.1, before being purified and sequenced. PCR products that consistently produced two bands were gel purified.

10.7 Linkage of Hidradenitis Suppurativa to 6q25.2

The genome-wide linkage screen using 400 fluorescently labelled primers on a number of families resulted in two candidate regions for HS susceptibility. These two regions were found on separate chromosomes indicating that HS is a genetically heterogeneous disease [64].

The first area of linkage was found to the long arm on chromosome 6 (band 6q25.2). Linkage was originally found in Family M with three markers after screening all affected and unaffected members. As HS can have a variable severity and age of onset the genome screen was originally performed only on the members of the family that were definitely affected. This original screen revealed a number of candidate loci where all the affected individuals shared alleles with certain markers. Linkage analysis was then carried out with unaffected members of the family using only the previously linked markers. A number of markers were uninformative and therefore high-density markers were run in order to eliminate these regions. This eliminated all markers except for one that co-segregated with the disease and initially gave a positive LOD score of 2.2 at recombination factor (θ) of 0 with D6S441. The first unlinked proximal and distal markers were used to define the boundaries of the candidate region that was between markers D6S308 and D6S1581. Genotyping was then performed using high-density markers from the ABI High Density 5 cM panel and extra markers ordered using sequence data on the UCSC website to further define the region. Recombinants with markers D6S440 and D6S442 defined the region as a 3.74-cM region on 6q.25, with a maximum two-point LOD score of 2.83 in Family M obtained with marker D6S1577. The fluorescent markers covering this region were then run on a number of other families with HS. Only one additional family, Family 6, appeared to be linked across this region. Family 6 gave positive LOD score with all markers run, with a highest combined two-point LOD score of 4.0 with marker D6S290. New DNA samples were obtained from members of Family M, which were then used to further screen the candidate region. Recombination events occurred with individual III.6 at D6S1577 and D6S441 and with a number of individuals with D6S440, narrowing the region to only 0.53 cM. This region contained six confirmed genes and one predicted gene according to the Human Genome Browser (UCSC Genome Bioinformat-

ics). These were ESR1, SYNE-1, FLJ21269, VIP, FBX05, MTRF1L and RGS17. The predicted exons for all of the genes were sequenced and possible alternative exons obtained from expressed mRNA data.

10.8 Identification of a Second HS Locus to Chromosome 19

A genome-wide scan was performed on DNA from 13 members of Family 13; 9 with HS and 7 unaffected. A cluster of markers on chromosome 19 co-segregated with the disease giving a highest two-point LOD score of 3.66 at recombination fraction with D19S414 (Table 2.18). Higher density markers were then taken from data on the Human Genome Browser and were run on the samples from Family 13 in order to define the limits of the candidate region. Recombination events narrowed the region to a 16.8-cM region between D19S911 and D19S1170 over the centromere of chromosome 19. The region contains 15 known genes and 6 predicted genes.

10.9 Candidate Genes Analysed in Linked HS Kindreds

10.9.1 Oestrogen receptor-α and HS

The apparent hormonal influence of HS made the oestrogen receptor-α a good candidate gene. HS symptoms usually begin post puberty and the average age of onset is early to mid-twenties. There have only been a few reports of prepubertal HS and these cases have usually been associated with precocious puberty or a hormonal imbalance [42]. Women are significantly more frequently affected by the disease then men and also often describe a premenstrual flare of the disease [25]. Symptoms tend to improve after the menopause [61]. There were however no obvious differences in hormone levels between patients and controls [2] suggesting that any hormonal influence may take place at the receptor level.

The physiological effects of oestrogen are mediated by the oestrogen receptor, a member of the nuclear receptor superfamily of transcription factors [34, 56, 62]. Oestrogen is known to exert an effect on reproductive activity but is also involved in the circulatory system, bone reabsorption and immune system. Oestrogens have significant effects on the skin and administration of oestrogen has been correlated with proliferation of basal cells in the epidermis and increased production of collagen [44, 55]. The increased oestrogen concentration affects secondary sexual characteristics in both males and females as large doses of oestrogen can increase or reduce the size of sebaceous glands and also apocrine sweat glands [44, 55]. An abnormality in the sizes of these glands has not been reported in HS but one report has demonstrated that the hair follicles in HS patients were larger than normal [28]. Oestrogen is involved in the production of pubic hair and both receptors are expressed in the hair follicle, and therefore may also exert an influence on the size of the hair follicles and contribute to the pathogenesis of HS [55]. It is therefore expressed in the appendages involved in HS and a mutation in one of these receptors could give a tissue-specific phenotype. This may be possible due to the presence of a large number of differentially expressed 5' regions that are hypothesized to give the receptors tissue specificity.

Polymorphisms were discovered in the ER-α gene of HS patients demonstrating that both genomic alleles were present. However, one or a small number of exons might be deleted and thus escape detection using an exon by exon PCR strategy. Southern analysis or long-range PCR can detect such deletions. Obtaining mRNA from affected individuals carrying heterozygous exonic polymorphisms would also reveal whether both alleles were being expressed.

10.9.2 ZNF91 and HS

Zinc finger protein 91 is a repressor of the IgG receptor FcγRIIB promoter. FcγRIIB is an inhibitory receptor that contains a tyrosine-based inhibition motif that is expressed on B-cells, macrophages, dendritic cells and mast cells [53]. Co-aggregation of FcγRIIB with the B-cell anti-

gen receptor (BCR) in mature or activated B-cells leads to inhibition of a number of cellular responses such as cell proliferation, antibody production and activation, and instead promotes apoptosis, whereas co-aggregation of FcγRIIB with FcεRIIB receptor in mast cells leads to an inhibition of antigen-induced degranulation and cytokine production [45]. ZNF91 is highly expressed in T lymphocytes and acts to repress FcγRIIB expression in these cells. Deficiency of FcγRIIB in mice leads mainly to susceptibility to autoimmune disease.

Here, screening of the ZNF91 gene revealed no mutations. As no polymorphic variants were identified in the ZNF91 gene it is impossible to conclude whether both alleles are present in HS patients. Haploinsufficiency of ZNF91 may cause HS by lifting the repression on FcγRIIB leading to an inhibition of cell proliferation.

10.9.3 TIZ Association with HS

TIZ emerged as one of the genes with real potential as a candidate for HS. TIZ inhibits TRAF6, a tumour-necrosis-factor- (TNF-) associated factor that is a signal transducer in the TNF receptor superfamily pathway, and also mediates nuclear factor kappa B (NF-κB) and JNK activation in the interleukin-1 receptor/Toll-like receptor (IL-1R/TLR) signalling pathway. NF-κB together with activator protein 1 are activated in acne lesions with consequent elevated expression of their target gene products, inflammatory cytokines and matrix-degrading metalloproteinases [31]. TRAF6 deficiency in mice illustrates its role in immune and inflammatory response. These mice showed a defect in normal B-cell differentiation, lymph node organogenesis, IL-1 signalling and lipopolysaccharide signalling. The mice, generally, showed features of hypohidrotic ectodermal dysplasia (HED) due to sweat gland, hair and dental abnormalities. This phenotype is not associated with HS but TNF and IL-1 signalling pathways have been implicated in playing a role in the disease. A gain-of-function mutation or dominant negative mutation in the TIZ gene may act in a different manner than a knockout of TRAF6. The effects of such a TIZ mutation might therefore be more specific, for example affecting only the development of appendages. Abnormally developed hair follicles would be likely to play a role in HS as illustrated by the report that hair follicles in HS patients were abnormally dilated and the epidermis surrounding the area was slightly thickened [28].

10.9.4 Potential Contribution of the VIP Gene to HS

TNF, as previously mentioned, activates a number of proinflammatory cytokines including vasoactive intestinal peptide (VIP), which is located within the chromosome 6 candidate region [59]. VIP is a 28-amino-acid regulatory peptide that is widely expressed in the nervous system and other tissues such as lung and skin. It plays a role in a wide variety of functions such as neurotransmission, neuroprotection and is a modulator of growth, survival and differentiation [23]. Other research has shown that VIP can in fact increase the production of inflammatory cytokines TNFα, IL-3, IL-1β, IL-6, granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) [9, 27]. Inflammatory cytokines can stimulate VIP synthesis, which can in turn inhibit these same cytokines in a negative feedback system illustrating its immunoregulatory function. VIP is highly expressed in the skin and is found in the sebaceous gland and sweat gland of the pilosebaceous unit and a mutation in VIP could potentially cause an inflammatory and immune disease such as HS [5, 30]. It is expressed in the appendages involved in HS and is involved in signalling in the immune and inflammatory response. Although these are thought to be coincidental secondary features of HS, they may cause obstruction and an aberrant immune response by activating or inhibiting downstream effectors in these pathways.

10.10 Additional Candidate Gene-Protein Systems in HS

10.10.1 Interleukin 1-α

Comedogenesis, which is a feature in HS, may be caused by high levels of interleukin 1-α [17]. Acne vulgaris is frequently associated and shares many similar features with HS. Both are described as diseases of follicular obstruction. The infundibulum of comedones in acne vulgaris patients possesses a thicker cornified layer than normal. The cells have thickened cell membranes which are sloughed off as a section of compacted cells that causes the keratinous plug within the follicular duct [35]. Guy and Kealey used isolated pilosebaceous infundibulum, maintained in medium, to demonstrate the response to certain proinflammatory cytokines [24]. Administration of IL-1α resulted in early cornification and hyperproliferation of infundibular keratinocytes that caused scaling of the lumen. They hypothesized that overexpression of IL-1α may lead to the abnormal cornification seen in comedones. IL-1α overexpression may be responsible for the initiation of inflammatory events leading to the hyperproliferation of the follicular lumen and resultant comedo that is observed in acne vulgaris and HS. Genes involved in the stimulation of IL-1α could therefore be responsible for the initial pathogenic events occurring in HS.

10.10.2 TNF Signalling and HS

Members of the TNF family are critically involved in host defence and immune responses and often mediate either apoptosis or cell survival. Anti-TNFα therapy has been shown to improve symptoms in some HS patients. In the first of these cases HS was a secondary disease treatment being given for Crohn's disease (OMIM 266600) or the inflammatory spondyloarthropathies such as ankylosing spondylitis (OMIM 183840). Both inflammatory diseases responded to anti-TNFα therapy. Both Crohn's disease and ankylosing spondylitis susceptibility loci show linkage to the same region on chromosome 19 as the HS gene [37, 47]. Another inflammatory disease susceptibility gene that maps to 19p13 is psoriasis (OMIM 605364). Psoriasis has also been associated with spondyloarthopathies and responds to infliximab, an anti-TNFα agent [33]. This implies there may be a common genetic predisposition to all these diseases as both Crohn's disease and inflammatory arthritis have an association with HS and all show genetic linkage to the same region on chromosome 19 [3, 11, 12, 21, 26, 32, 40, 48, 49, 50, 57].

10.11 Discussion

Two regions have been identified that are possible loci for HS. One of these loci, on chromosome 6, yielded a statistically significant 2-point LOD score when the linkage data from two families were combined. This locus should therefore be treated with caution since it would be preferable to obtain a significant LOD score of >3.0 using data from one family only, so that there is less likelihood of any spurious linkage effects. Nevertheless, the known genes within the chromosome 6 locus have been fully sequenced without the identification of any potentially pathogenic mutations. Other genes in this region may yet be discovered as there are human mRNA sequences aligned to 6q25.2 that do not correspond to any of the known genes and may turn out to be expressed genes that are as yet unknown.

The region of chromosome 19 spanning the centromere constitutes the second candidate region. This locus gave a statistically significant LOD score with data from one family and therefore represents a more robust linkage result than the 6q locus. This linked interval contains at least 21 genes, some of which have an unknown function and some that are predicted proteins. Only seven genes were chosen whose function or homology to other proteins made them good potential candidate HS genes. No mutations were found in any of these genes but there are still a number of other genes to screen that may carry a mutation. In addition, the causative mutation may have been missed, as discussed below.

A number of other, smaller families and sporadic cases that were too small on which to perform a genome-wide screen did not show linkage to either of the candidate loci described here. Although HS is now known to be a heterogeneous disease it appears that it may be caused by mutations in genes at multiple locations making it a more complex disease than originally thought.

The linkage to chromosome 6 was narrowed down by recombinants to a small region of 6q25.2 containing only six genes. The genomic structure of each of these genes was established using sequence data from the Human Genome Browser, April 2003 freeze. Any potential alternative exons encoding a different isoform or splice variant were obtained from gene prediction programs such as Genescan and Twinscan that were annotated on the Human Genome Browser. Human aligned mRNA sequences were also used for potential new spliced isoforms. Each of the genes was analysed by PCR and direct sequencing. Although a number of sequence changes were detected, these either did not segregate with the disease phenotype and/or were detected in normal controls, and therefore no mutations were discovered.

Another HS family linked to the centromeric region of chromosome 19 between markers D19S911 and D19S1170. This region includes 19p13.11, 19p12, 19p11, 19q11 and 19q12 cytogenetic bands and covers 16.8 Mb of genomic DNA but contains only 14 known genes and 7 predicted genes. There were also several *in silico* predicted genes in the interval. There are a high percentage of zinc finger proteins in this region and is therefore composed of very repetitive sequences which often causes problems in the ability to specifically amplify genes. A large number of genes in these regions are involved in the immune and inflammatory response by activating or inhibiting proinflammatory cytokines. The cytokines involved, such as IL-1, IL-10, IL-6 and TNF, have roles in the development of epidermal appendages, hyperproliferation and cornification of epidermal cells and initiation of immune signalling [6, 14, 15, 17, 24, 29, 38]. Therefore, a mutation in any of the genes controlling these functions could potentially underlie HS. A candidate gene approach was taken in screening some of these genes, in particular those that had potential due to their expression pattern or function. Seven genes were fully sequenced to date in the chromosome 19 region but the pathogenic mutation responsible for HS has not yet been found [64].

10.12 Conclusions

Although all the genes in the chromosome 6 candidate gene were sequenced no mutations were discovered. This implies that there may be more genes in this region that have yet to be identified, although analysis of the human mRNAs expressed here reveals only a few other aligned mRNA sequences that did not correspond to the known genes. The mutational analysis we performed was PCR-based and this method could have failed to detect any genomic deletions that could cause haploinsufficiency or larger in-frame and potentially dominant-acting deletions. Obtaining skin biopsy samples from patients and quantifying the expression of these genes by quantitative RT-PCR to accurately measure expression of alleles could overcome this problem. Seemingly benign missense mutations and polymorphisms should also not be overlooked. These types of changes have recently been discovered to affect splicing and have been shown to cause breast cancer and cystic fibrosis [39, 46].

The candidate region on chromosome 19 covered a large area, 16.8 Mb of genomic sequence. There were relatively few genes in comparison to the size of the region and the fact that chromosome 19 is one of the most gene-rich chromosomes [58]. The candidate region links over the centromere and the regions immediately adjacent to the centromere are not predicted to contain many genes. The linked region, defined by markers D19S911 and D19S1170, was rich in ZNF genes and chromosome 19 has the highest repeat density [58]. The majority of the ZNF proteins are highly expressed in T lymphoid cells, B-cells

and monocytic and erythroid cells. Although the functions of most are unknown, as a whole, ZNF proteins are thought to be involved in development. ZNF91 has been shown to function as a repressor of an IgG receptor and therefore has an influence on the immune response as do some of the other candidate genes studied, such as TIZ. No mutation was found in any of the candidate genes analysed but there are a number of genes still to be sequenced. In addition to the known genes, mRNA alignment and gene predictions reveal that there may still be some genes that are as yet unidentified.

In conclusion, the first two candidate genetic loci for HS have been identified and this will form the basis of future genetic studies, using other families with clearly defined dominant inheritance, to narrow down these loci and identify the causative genetic lesions. Importantly, a number of other families do not link to either locus. These families were too small to perform genome-wide linkage analysis but it demonstrates that HS is indeed a genetically heterogeneous disease with potentially three or more genes involved in its molecular pathogenesis. The eventual identification of these causative genes will undoubtedly be of benefit in understanding the pathomechanisms of HS and form the basis for a rational design of new therapeutic strategies.

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Chapter 11

Bacteriology of Hidradenitis Suppurativa

11

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Key points

- The pathogenesis of hidradenitis suppurativa (HS) is still poorly understood and not yet clearly defined
- A large variety of bacteria can be found in HS lesions and many of them belong to the normal flora of the skin
- In the studies using the bacteria prevalent on the surface of the lesions there is possible contamination from the resident flora of the skin
- In cases of cultures obtained from the deeper parts of HS, *Staphylococcus aureus*, coagulase-negative staphylococci and anaerobic bacteria have commonly been isolated
- The first event seems to be follicular occlusion by keratinized stratified squamous epithelium in apocrine-bearing areas, with subsequent inflammation
- The initial inflammatory change can be produced by a pyogenic bacterial infection or by factors similar to those involved in acne
- In chronic lesions, bacteria represent a risk factor for the destructive scarring and extension of the disease and secondary bacterial infections may occur
- Antibiotics do not cure the disease but they may relieve the symptoms through either an antibacterial or an anti-inflammatory effect

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11.1 Normal Microflora of the Skin

Normal human skin is colonized by a large variety of organisms that live as commensals on its surface. There are quantitative differences among different regions of the skin, related to temperature difference, moisture content, and the presence of various amounts of skin lipids that may be inhibitory or lethal for some microorganisms. These differences characterize three main regions of the skin: (1) axilla, perineum, and toe webs; (2) hands, face, and trunk; and (3) arms and legs [20]. The skin microflora reside on the skin surface and in the ducts of hair follicles and sebaceous glands [38].

Table 11.1. The most important genera and species of bacteria normally found on the skin

Genus	Characteristics	Most prevalent species
Coagulase-negative *Staphylococcus*	Aerobic, Gram-positive cocci	*S. hominis, S. haemolyticus* *S. epidermidis*
Micrococcus	Aerobic, Gram-positive cocci	*M. luteus, M. varians*
Corynebacterium	Aerobic, Gram-positive pleomorphic rods	*C. bovis, C. minutissimum*
Propionibacterium	Anaerobic, Gram-positive rods	*P. acnes, P. granulosum, P. avidum*
Acinetobacter	Aerobic, Gram-negative coccobacilli	*A .calcoaceticus* var. *lwoffi* and var. *anitratus*

The sites affected by HS are, in order of frequency: axillary, inguinal, perianal and perineal, mammary and inframammary, buttock, pubic region, chest, scalp, retroauricular, and the eyelid [50].

The major groups of microorganisms present on the skin are various genera of bacteria and yeasts. The predominant bacteria of the skin are as follows (Table 11.1) [20, 21]:

- Coagulase-negative staphylococci
- Micrococci
- Saprophytic *Corynebacterium* species (diphtheroids)
- *Propionibacterium* species
- *Acinetobacter* species.

Various coagulase-negative staphylococci are found on the skin and some have special predilection for some areas, for example *Staphylococcus hominis* and *Staphylococcus haemolyticus* are found principally in areas where there are numerous apocrine glands, such as axillae and the pubic region [20, 32]. *Staphylococcus epidermidis* is also an important resident, colonizing moist areas of the skin [21]. It is found preferentially in the upper part of the body and represents over 50% of the resident staphylococci [47].

Micrococcus species are found on the skin, especially in women and children, and *Micrococcus luteus* and *Micrococcus varians* are the prevailing species [20, 21]. These microorganisms often colonize axilla, perineum, and groin [21].

Different bacteria belonging to the genus *Corynebacterium* are associated, but not exclusively, with moist areas of the skin [21].

Propionibacteria are Gram-positive rod-shaped anaerobic bacteria. *Propionibacterium acnes* and *Propionibacterium granulosum* are associated with follicles that have large sebaceous glands on the face and upper trunk and they have a role in acne pathogenesis. *Propionibacterium avidum* is found in moist areas (axillae and groin) and it is not known if it has pathogenic potential [21].

Acinetobacter species are the only important Gram-negative residents of the skin and are found in the axillae and groin of 25% of the population [21].

In addition, any bacterial species that is found in nature or belongs to the normal flora on noncutaneous areas may temporarily be found on the skin [47]. *Staphylococcus aureus* is not normally considered a resident of normal skin, but it can be found on perineal skin, axillae, and in the toe cleft. Hemolytic streptococci may be found as transients on different skin sites, more often in children [38]. Atypical mycobacteria may be found in genital and axillary regions and *Bacillus* species or different Gram-negative bacilli such as *Proteus*, *Pseudomonas*, *Enterobacter* and *Klebsiella* are rarely found on the skin [20, 38].

In conclusion, a large variety of bacteria are able to colonize the most affected areas in HS: axilla, perineum, and the groin.

11.2 Bacteria Found in HS Lesions

Although the HS etiology is unknown, a large variety of microorganisms can be isolated from the lesions. The clinical picture of the disease resembles an infectious process and various

Table 11.2. Studies describing the diversity of bacteria found in various HS lesions

Investigator	Bacteria found	Area of the skin
Leach et al. [35]	*Staphylococcus aureus,* anaerobic bacteria	Axillae
Brenner and Lookingbill [7]	*Staphylococcus aureus, Staphylococcus epidermidis Bacteroides fragilis, Bacteroides melaninogenicus*	Perirectal, groin, axillae
Highet et al. [23]	*Streptococcus milleri*	Perineal
Highet et al. [24]	*Streptococcus milleri, Staphylococcus aureus*, anaerobic streptococci, *Bacteroides* species	Perineal
Finegold et al. [18]	*Biophila wadsworthia*	Axillae
Bendahan et al. [5]	*Chlamydia trachomatis*	Perineal
Jemec et al. [29]	*Staphylococcus aureus, Streptococcus milleri, Staphylococcus epidermidis, Staphylococcus hominis*	Axillae, groin, breasts, buttocks
Brook and Frazier [8]	*Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa*; *Peptostreptococcus* species, *Prevotella* species, micro-aerophilic streptococci, *Fusobacterium* species, *Bacteroides* species	Axillae
Lapins et al. [33]	*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, group B hemolytic streptococci, group C hemolytic streptococci, *Bacillus cereus*, diphtheroides, enterobacteriacae-; *Peptostreptococcus* species, *Propionibacterium acnes,* microaerophilic streptococci, *Lactobacillus* species, *Bacteroides fragilis,* other *Bacteroides* species, *Prevotella* species	Axillae and perineal

bacteria are suspected as being responsible for the inflammation. The bacterial findings are considered by some authors as either contaminants from the normal skin flora or a result of secondary infection in a previously sterile process [33].

Despite the volume of the discharge the HS lesions are often found to be sterile [29, 33], but sometimes a large variety of microorganisms can be isolated from the sinuses, particularly staphylococci, streptococci, Gram-negative rods, and anaerobic bacteria (Table 11.2). The bacterial flora are not consistent and may change unpredictably [31]. Brook and Frazier [8] found, in a retrospective review of clinical and bacteriological data from patients with axillary disease, that the most prevalent aerobic bacteria were *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* and the most frequent anaerobic bacteria were *Peptostreptococcus* species, *Prevotella* species, microaerophilic streptococci, *Fusobacterium* species, and *Bacteroides* species.

In most of the studies samples are collected from the surface of the lesions [22–24] and there is a high risk of contamination with the resident skin flora. In these conditions the bacteriological results are difficult to interpret. Jemec et al. [29] have aspirated pus from the deeper parts of HS. Bacteria were found in half of active lesions: *Staphylococcus aureus* and coagulase-negative staphylococci (*Staphylococcus epidermidis* and *Staphylococcus hominis*) were most commonly isolated. An explanation for the large number of negative cultures could be that it is difficult to localize the infected part using the aspiration technique. It was found that the duration of the disease was shorter for those patients in whom *Staphylococcus aureus* was detected as a possible etiological factor, indicating that this bacterium may be involved early in the disease pathogenesis by causing anatomical changes in the hair

Table 11.3. Possible factors responsible for coagulase-negative staphylococci pathogenicity in HS lesions

Factors	Effect
Sinus formation in HS lesions	Enhances the pathogenic properties of the bacteria [33]
Bacterial capacity of biofilm formation	Protects against antibiotics and from attacks by the immune system [42]
Bacterial production of lipases, proteases, and other exoenzymes	Persistence in the host. Tissue degradation [42]
Toxin production	Invasion properties [35, 36]
Production of PAS-positive extracellular polysaccharide substance	Obstructs the delivery of sweat to the skin surface [37]

follicles. These modifications may later predispose to inflammation independently of the presence of bacteria [29].

Lapins et al. [33] circumvented problems both of contamination and of missing the active area of infection by using a carbon dioxide (CO_2) laser surgical method to evaporate the diseased tissue level by level from the surface downwards. This allows sampling for bacteriological cultures from each level without the risk of contamination with bacteria from the level above. By using this method, bacteria were found even in the deeper and closed parts of HS. *Staphylococcus aureus* and coagulase-negative staphylococci were also the most commonly found species. After the *Staphylococcus* species the most commonly cultured bacteria were the anaerobic species found in the deeper levels: *Peptostreptococcus* species and *Propionibacterium acnes*. The aerobic bacteria were found in 60% of positive cultures at deep levels.

The clinical significance of coagulase-negative staphylococci is unclear because while they are part of the normal microflora [29, 33] they have also gained attention as pathogens (Table 11.3). Coagulase-negative staphylococci are associated with infections in those with intravascular catheters [46] and prosthetic devices [14] where the presence of the foreign body will increase the pathogenic properties of these otherwise harmless members of the normal flora. Lapins et al. [33] have often found coagulase-negative staphylococci as the sole bacteria in the deep portion of the lesions and suggested that the abnormally structural tissue in HS due to sinus formation can provide a medium similar to the presence of a foreign body and the result will be enhancement of the pathogenic properties of coagulase-negative staphylococci. Generally, the pathogenic potential of coagulase-negative staphylococci is mainly due to their capacity to form biofilms on medical devices [42]. The sinus formation in HS may be an ideal place for biofilm formation and this microbiologic principle may be applicable to coagulase-negative staphylococci in HS. Many coagulase-negative staphylococci produce several lipases, proteases, and other exoenzymes, which possibly contribute to the persistence of coagulase-negative staphylococci in the host and may degrade host tissue [42]. Here, the bacteria find protection against antibiotics and from attacks by the immune system. The biofilm model was recently proposed to be involved in acne pathogenesis, where glycocalyx polymer secreted by *Propionibacterium acnes* as a biofilm may explain the immunogenicity of the organism as well as the unpredictable course of the disease [11]. There are also some lines of evidence that under certain conditions they may produce similar toxins to *Staphylococcus aureus* and could cause invasive diseases [36, 56].

Mowad et al. [37] showed that periodic-acid-Schiff- (PAS-) positive extracellular polysaccharide substance produced by *Staphylococcus epidermidis* obstructs the delivery of sweat to the skin surface and these strains are involved in the pathogenesis of miliaria. It was speculated that a similar mechanism could be involved in HS pathogenesis [33]. It is known that the pathogenic potential of coagulase-negative staphylococci varies according to species [33]. *Staphylococcus haemolyticus* and *Staphylococcus saprophyticus* have well-known pathogenic potential and *Staphylococcus lugdunesis*, *Staphylococcus schleiferi* or *Staphylococcus caprae* are considered emerging pathogens [56]. *Staphylococcus lugdunesis* was found in axillary lesions diagnosed as HS [54].

Streptococcus milleri, a microaerophilic microorganism frequently causing pyogenic infections [17] that often colonizes the gastrointestinal tract and female genital tract, was found by some investigators to be a major pathogen in perineal HS. Furthermore, the presence of this bacterium correlated with the disease activity and its elimination by appropriate antibiotic therapy was accompanied by marked clinical improvements [23, 24]. Microaerophilic streptococci were found by Brunsting in 1939 in a group of patients with HS [9]. *Streptococcus milleri*, *Staphylococcus aureus*, anaerobic streptococci, or *Bacteroides* species were frequently isolated in a group of 32 patients with active perineal HS [24]. Other authors could not find *Streptococcus milleri* in any of the specimens [41].

In perianal forms of HS, *Escherichia coli*, *Klebsiella* and *Proteus* strains as well as anaerobic bacteria were isolated [27]. Brenner and Lookingbill [7] have recovered *Bacteroides* species from perirectal, groin and axillae and the patients responded well to a suitable antibiotic treatment regimen. They suggest that the presence of anaerobic bacteria may reflect the chronicity of pre-existing local infection. Anaerobic bacteria were also isolated by Leach et al. from recurrent axillary lesions of HS [35].

Bilophila wadsworthia is a Gram-negative anaerobic rod found as part of the normal flora in feces and, occasionally, in saliva and in the vagina; in one case of HS it was isolated together with other anaerobic bacteria of the *Prevotella* species [4, 18].

Bendahan et al. [5] found an association between perineal HS lesions and *Chlamydia trachomatis* infection, but it was not clear whether the latter was a direct cause or a predisposing factor. These findings have not been confirmed by other authors.

11.3 General Factors About Bacterial Involvement in HS Pathogenicity

The series of events in HS pathogenesis are unclear and the exact role of bacteria in the etiology of the disease remains controversial. Shelley and Cahn [49] were able to reproduce HS lesions by applying atropine-impregnated adhesive tape to a manually depilated axillary region. They noticed subsequent dilatation, inflammation, and bacterial invasion of the apocrine duct and concluded that HS is a bacterial infection of an obstructed apocrine sweat gland with the causative bacteria deriving from the normal flora of the skin.

However, today it is largely accepted that apocrine gland involvement is not essential to the pathogenesis, and that the inflammatory processes and involvement of apocrine glands are secondary events [6, 28]. The disease starts with follicular hyperkeratosis and dilatation of the infundibula and most authors believe that the bacterial contribution is a secondary event in the disease process [27, 48]. The retention of keratin in follicles and chronic sinusoids is subject to subsequent bacterial infection. Follicular occlusion leads to dilatation followed by rupture and spillage of the keratin and bacteria into the dermis. This induces a strong chemotactic response with an inflammatory cellular infiltrate consisting of neutrophils, lymphocytes, and histiocytes [50]. In chronic lesions, bacteria can be found in and around the glands and lymphatics [34]. In later stages of HS, bacterial infection is a risk factor for extension of the lesions. Sinus tracts are formed in the dermis and subcutis from the ruptured follicular epithelium in an attempt by the tissue to confine the inflammation, and there is a high risk for secondary infections [34, 50].

Systemic infections such as bacterial meningitis, bronchitis or pneumonia are possible, due to the spread of microorganisms [27]. In the case of coagulase-negative staphylococci, the recently found inflammatory peptides called phenol-soluble modulins (microbial products that stimulate cytokine production in host cells) play a role in the pathogenesis and systemic manifestations of sepsis [42].

Polypeptides from *Propionibacterium acnes* were found to stimulate a specific immune response in acne patients [26]. Jemec et al. [29] tried to detect a specific serologic response to a possible staphylococcal or streptococcal infection but the results were inconclusive.

11.4 The Role of Antibiotics in the Treatment of HS

Despite the fact that the clinical response to antibiotics is poor and that bacteria are found in only 50% of lesions, the recommendation for systemic antibiotics is clear and this is derived from empirical attempts to control the disease. Also, it is reasonable to try antibiotic treatment, as various bacteria are suspected as having a role in the inflammatory process and in destructive scarring in HS patients. Approximately 10% of patients have some benefit from the use of systemic antibiotics [57].

If the drainage from lesions is available, bacterial cultures and antibiotic sensitivity should be performed and the antibiotic treatment should be tailored according to these results. Collaboration between the dermatologist and the bacteriologist is an important factor in finding the best treatment option. Acute episodes and relapses are treated as bacterial infections for a 2-week period [21]. Oral antibiotics such as minocycline, erythromycin in combination with metronidazole, ciprofloxacin, cephalosporins or semisynthetic penicillins may be used [7, 19, 21]. Bukley and Sarkany [10] reported a case of severe HS who improved after systemic clindamycin treatment.

Long-term administration of tetracyclines or erythromycin may be used in regimens similar to acne vulgaris and seems to prevent episodic flares [19, 21].

Topical clindamycin was found to be superior to placebo in a randomized double-blind clinical trial [12] and Jemec and Wendelboe did not find any difference between systemic tetracycline and topical clindamycin in another randomized clinical trial [30]. However, after withdrawal of antibiotic treatment, HS very often relapses [3, 13].

As is the case with acne vulgaris, it is not known whether the most important factor in the treatment of HS is antibacterial or anti-inflammatory. Lincosamides and tetracyclines have been known for their immunomodulatory effects. Clindamycin suppresses the complement-derived chemotaxis of polymorphonuclear leukocytes in vitro, thereby reducing the inflammation potential [43, 52]. Tetracyclines are known as good candidates for the treatment of inflammatory disorders. The anti-inflammatory properties are enumerated in Table 11.4 [43, 44].

Table 11.4. Anti-inflammatory and immunomodulatory properties of antibiotics used in the treatment of HS

Antibiotic	Mechanisms
Tetracyclines	– Inhibition of metalloproteases – Inhibition of free radicals – Modulation of IL-1α – Inhibition of lipases and proteases – Inhibition of nitric oxide synthetase and caspase 1 and 3 production – Modulation of cytokine expression – Reduction in the production of free radicals secreted by polymorphonuclear leukocytes – Reduction in the formation of inflammatory granuloma
Clindamycin	– Suppression of complement-derived chemotaxis of polymorphonuclear leukocytes

Hindle et al. treated seven patients with a combination therapy of clindamycin (300 mg twice daily) and rifampicin (300 mg twice daily) for a 10-week period [25]. Three patients did not tolerate the combination, two because of diarrhea associated with *Clostridium difficile,* and three of them responded well and remained clear at 12 months. The combination of rifampicin and clindamycin was also successfully used for two other chronic and difficult-to-treat conditions: folliculitis decalvans [45] and acne keloidalis nuchae [25]. Clindamycin is a lincosamide antibiotic active against Gram-positive cocci (except enterococci) and most anaerobic bacteria [52]. Rifampicin is a broad spectrum antibacterial agent that inhibits the growth of the majority of Gram-positive bacteria as well as many Gram-negative microorganisms [55]. It is highly active against both *Staphylococcus aureus* and coagulase-negative staphylococci. Rapid emergence of resistance when the drug was used alone has limited the use except in association with another anti-staphylococcal drug [2]. The

combination therapy was introduced to prevent resistance development against rifampicin and to cover a broad antibacterial spectrum.

11.5 Possible Consequences for Bacterial Ecology due to Antibiotic Treatment in HS

The drawback to the usefulness of long-term antibiotic treatments is concern about the effect on microbial ecology (Table 11.5). The normal microflora act as a barrier against colonization by potentially pathogenic bacteria and the control of growth of opportunistic bacteria is called colonization resistance. The normal equilibrium between host and microorganisms may be disturbed by a number of factors, but commonly and essentially by antibiotic therapy. To what extent disturbances occur depends of numerous factors: the spectrum of the antibiotic, the dose, the route of administration, pharmacokinetic and pharmacodynamic properties and in vivo inactivation of the drug [53].

Clindamycin administration results in major ecological disturbances in intestinal and oropharyngeal microflora: the numbers of enterococcal species increase and those of all anaerobes decrease [39, 51]. A possible complication of clindamycin treatment is pseudomembranous colitis, which occurs when antibiotics such as clindamycin, ampicillin and third-generation cephalosporins suppress the normal flora, allowing *Clostridium difficile* to grow and produce toxins [40]. Rifampicin treatment was shown to lead to a decrease in total aerobic and anaerobic oral bacteria in healthy volunteers [1].

The emergence of antimicrobial resistance is strongly associated with the clinical use of the antibiotics and a balanced microflora prevents establishment of resistant strains of bacteria [53]. It is well known that oral antibiotics select for resistant bacteria at all body sites where there is a normal flora: skin, conjunctivae, oral cavity, nasopharynx, upper respiratory tract, intestinal tract, and vagina [16]. A therapy administered for a long period, as was recommended in HS treatment [25], will exert a high pressure for the development of the resistant strains of *Propionibacterium acnes*, coagulase-negative staphylococci on the skin, *Staphylococcus aureus* in the nares, streptococci in the oral cavity, and enterobacteria in the gut [16].

Table 11.5. Effects of antibiotic administration on the ecological balance of human microflora

- Disturbances in the balance between host and normal flora from the intestinal tract, skin, oropharyngeal tract, and vagina
- Altered colonization resistance (growth control of opportunistic bacteria)
- Overgrowth of pathogenic bacteria or yeasts
- The emergence of antimicrobial resistance in the normal flora
- Possible transfer of resistance to pathogenic bacteria

Topical clindamycin will increase carriage of *Propionibacterium acnes* and *Staphylococcus epidermidis* resistant strains on skin and there is a risk of transfer of resistance to other pathogenic bacteria, *Staphylococcus aureus* and *Streptococcus* species [15]. The skin and conjunctivae flora from untreated sites will also be affected by transfer of antibiotic [16].

In conclusion, antibacterial drugs represent an adjuvant treatment in HS. They are not curative but they reduce odor and discharge, and diminish pain. Antibiotics represent a palliative therapy that may control the disease in early stages and can reduce the inflammation before and after surgery [28] but clinicians should be aware about the downside of taking them.

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Chapter 12

Endocrinology

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12

Key points

- HS does not generally appear to be associated with signs of hyperandrogenism
- Sex hormones may affect the course of HS indirectly through, for example, their effects on inflammation
- The role of end-organ sensitivity cannot be excluded at the time of writing
- The prevalence of polycystic ovary syndrome in HS has not been systematically investigated

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12.1 Introduction

In 1986 Mortimer et al. [14] reported that hidradenitis suppurativa (HS) responded to treatment with the potent antiandrogen cyproterone acetate. They suggested that the disease could be androgen-dependent [8]. This hypothesis was also upheld by occasional reports of women with HS under antiandrogen therapy [18]. Actually, the androgen dependence of HS (similarly to acne) is only poorly substantiated.

12.2 Hyperandrogenism and the Skin

Androgen-dependent disorders encompass a broad spectrum of overlapping entities that may be related in women to the clinical consequences of the effects of androgens on target tissues and of associated endocrine and metabolic dysfunctions, when present.

12.2.1 Androgenization

One of the less sex-specific effects of androgens is that on the skin and its appendages, and in particular their action on the pilosebaceous unit. Hirsutism is the major symptom of hyperandrogenism in women. Other dermatological conditions include acne and the chronic hair loss usually termed androgenic alopecia (AGA). Whereas acne, hirsutism and chronic hair loss may coexist in the same patient, it is not unusual to find only one of these androgenic manifestations [16].

Depending on the presence of ovarian dysfunction, extracutaneous manifestations may include abnormalities of menstruation with

anovulatory patterns, oligomenorrhoea, fertility problems, android obesity and risks for metabolic complications, such as hyperinsulinism, insulin resistance, diabetes mellitus, and dyslipidaemia, and for cardiovascular diseases [6, 16].

12.2.2 Androgen Metabolism

The causes of hyperandrogenism are multiple (Table 12.1). Skin androgenization in women may be due to abnormal production of androgens by the ovaries and/or the adrenal glands, and/or to an excessive response of target cells in the pilosebaceous unit (peripheral androgenism) [6].

Androgens [testosterone and the less potent androgens in women Δ4-androstenedione (Δ4A) and dehydroepiandrosterone (DHEA)] are synthesized by the adrenals (mostly DHEA and its sulfate – SDHEA) and the ovaries (mostly Δ4A) and may be subsequently transformed into oestrogens through the aromatization of the molecules. Sex hormone binding globulin (SHBG) synthesized in the liver is the major carrier protein for androgens and oestradiol. Only free androgens, unbound to SHBG, are directly active on target cells. In tissues, androgens are first metabolically transformed into the active form dihydrotestosterone (DHT), which then binds to androgen receptors (AR) [16].

Table 12.1. Causes of hyperandrogenism

1. Polycystic ovary syndrome (PCOS)
2. Non-classic adrenal hyperplasia with 21-hydroxylase deficiency
3. Skin hypersensitivity = peripheral hyperandrogenism:
   - with hirsutism (idiopathic)
   - and/or acne or androgenic alopecia
4. Drugs
   - androgenic progestins
   - OP contraception with androgenic progestins
5. Others (rare):
   - adrenal and ovarian tumours
   - Cushing's syndrome

Sebaceous glands, but also keratinocytes from the acroinfundibulum and dermal papilla cells, can synthesize androgens de novo from cholesterol or by locally converting weaker androgens (Δ4A and DHEA) to testosterone and DHT. As in other classic steroidogenic organs, the pilosebaceous unit expresses the major enzymes involved in androgen metabolism, namely steroid sulfatase, 3β-, 3α- and 17β-hydroxysteroid dehydrogenases, and 5α-reductase, which converts testosterone into DHT. Furthermore aromatase, which converts testosterone into oestradiol, is localized to sebaceous glands and to both outer and inner root sheath cells of anagen terminal hair follicles. This hormone may play a "detoxifying" role by removing excess androgens [5].

12.2.3 Causes of Hyperandrogenism

As far as hyperandrogenisms due to an excess of androgen production are concerned, tumoral causes and Cushing's syndrome are rare. The most common endocrine disorders are polycystic ovary syndrome (PCOS) and non-classic adrenal hyperplasia (NCAH) with 21-hydroxylase deficiency. Hyperandrogenism is associated with high levels of circulating androgens and decreased SHBG levels. PCOS also requires morphological and ultrasound criteria: an increased number of subcapsular follicles and stromal hyperplasia. Plasma levels of 17-hydroxyprogesterone (17-HP) are increased in NCAH. If NCAH is only suspected with moderately increased 17-HP, an adrenocorticotropic hormone (ACTH) test must be performed [1, 6, 7].

On the other hand, hyperandrogenic skin changes ("idiopathic" hirsutism, hypertrichosis in men, most cases of acne, AGA in women but also in men) mostly occur in fact in patients with normal androgen levels. Increased enzyme activities in the peripheral metabolism of steroids, and/or increased sensitivity of AR, both presumed to be subjected to genetic polymorphisms, might account for abnormal responses to androgens. The first possibility in patients with androgen-dependent skin manifestations corresponds to increased metabolic pathways that lead to the transformation of weaker an-

drogens to testosterone, increased 5α reduction to DHT and lower aromatase activity [16].

The second possibility (the two not being mutually exclusive) is directly linked to AR sensitivity. AR is a structurally conserved member of the nuclear receptor superfamily. The amino-terminal domain is required for transcriptional activation and contains a region of polyglutamine encoded by CAG trinucleotide repeats. In humans the number of CAG repeats is polymorphic. Longer repeat lengths are associated with androgen-insensitivity syndromes. It has been suggested that AR polymorphisms (CAG-repeat lengths) account for AGA, hirsutism and acne, since shorter repeat lengths may be associated with the development of androgen-mediated skin disorders in men and women [17].

12.3 Lack of Association between HS and Endocrinopathies

Although HS has been reported in two men with acromegaly [4], which is very likely due to a direct effect not of androgens but of growth hormone on apocrine glands, HS was not found to be associated with endocrine disorders.

In women HS has not been reported in association with ovarian or adrenal tumours, Cushing' syndrome, PCOS or NCAH, all known causes of hyperandrogenism with increased or abnormal androgen production. In fact, a possible association of HS with functional hyperandrogenism (ovarian or adrenal dysfunction) merits investigation with modern biological and ultrasound markers [7].

HS usually begins after puberty when the apocrine glands are fully developed. A few cases have been reported in children, as clinical manifestations of premature adrenarche or early puberty [11, 12, 15]. This represents in fact the strongest evidence for an influence of androgens on HS. However, HS is more common in women and usually affects premenopausal women, although it may appear after menopause [3]. The rare incidence of HS in postmenopausal women does not stand in favour of a role for androgens, since hyperandrogenism after the menopause has yet to be demonstrated. On the other hand, improvement during and relapse after pregnancy, as well as premenstrual and menstrual exacerbations are usually noted, suggesting that hormones, at least oestrogens, may influence the course of the disease. Oestrogens in fact are known to interfere with inflammatory processes, independently of a direct genomic action of the steroids. This could account for their influence on the natural course of inflammatory diseases, such as acne, but also HS. Other observations in HS in terms of premenstrual and/or menstrual exacerbations may be unrelated to the oestrogen or androgen dependency of the disease.

Although HS may be associated in some women with classic signs of skin androgenization such as acne and/or hirsutism, no real association of HS with hirsutism (the major symptom of hyperandrogenism) has ever been reported. In a series of 70 women with HS, acne was not more frequent than in controls [10]. The incidence of patients with signs of androgenization did not differ significantly between the two groups. Only a shorter menstrual cycle and a longer duration of menses in patients with HS were noted. Although there was no evidence in favour of or against an association with PCOS or with NCAH, these data indicate that HS is not accompanied by the usual clinical signs of androgenization.

12.4 HS and Biological Hyperandrogenism

Furthermore, as far as serum levels of androgens and SHBG are concerned, there is no clear evidence for biochemical hyperandrogenism. On average, androgen levels (total plasma testosterone and free testosterone index due to a low SHBG) were increased, but were normal in many individual patients, and no significant decrease of SHBG could be detected [13]. In fact, SHBG is known to be regulated by factors that influence body weight and this study was not controlled for body weight, and neither was a second one which found hyperandrogenism in a subgroup of women who did not experience a premenstrual flare in their disease [9]. In a further group of 66 women with HS, among which 23 had acne, 23 were significantly obese and 19

were hirsute; testosterone and DHEAS were normal in all subjects [3]. In obese subjects, SHBG was reduced, consistent with body-mass-index-matched controls. No evidence for biochemical hyperandrogenism could be found in women with HS when compared with controls matched for age, weight, and hirsuteness [3].

12.5 End-Organ Androgen Sensitivity?

All the above data suggest that the main mechanism for the possible role of sex hormones in HS lies in end-organ sensitivity rather than in the plasma levels. Women can develop HS while taking oral contraceptives especially when androgenic progestins are used, and this also suggests, as in acne, a possible androgen dependence of the disease [19]. In acne, not only sebocytes but also other epithelial cells are involved in the "skin hyperandrogenism" that is responsible for the formation of the comedo. Keratinocytes from the acroinfundibulum express the key enzymes involved in the in situ metabolism of androgens (in situ synthesis of the weaker androgens, their transformation into testosterone and its reduction into DHT) [5]. Investigation for the activity of these enzymes in the epithelial cells that are presumed to be involved in the first stage, i.e. follicular occlusion, of HS remains to be conducted.

However, androgen metabolism has been investigated in normal human apocrine glands and in those isolated from age-matched patients with HS [2]. No increased activity of 3β-hydroxysteroid dehydrogenase, Δ4-5 isomerase, or 17 β-hydroxysteroid dehydrogenase was found and 5α-reductase activity was similar. These results suggest that HS cannot be attributed to exaggerated activities of androgen-interconverting enzymes within apocrine gland cells.

These data should not be interpreted as reflecting a lack of apocrine sensitivity to androgens, since they relate to the quantity of active metabolite (DHT) and not to the androgen response at the receptor level. It cannot be excluded that there is increased sensitivity of cellular AR, due to genetic polymorphism of the receptor, that might account for the as yet hypothetical skin hyperandrogenism in women with HS. On the other hand, a genetic polymorphism in enzyme activities at the epithelial cell level remains to be demonstrated. Finally, in the absence of precise investigations, based upon biological markers (testosterone, Δ4A, 17-OHP, SHBG levels, free testosterone index) and ovarian echography [1, 7], the possibility that some women with HS suffer from PCOS or NCAH cannot be excluded.

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Chapter 13

Immunity

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13

Key points

- The epidermis has a powerful innate immune system
- Keratinocytes are immunologically active cells, able to identify and kill invading microbes by recognizing highly conserved structures of the pathogens (pathogen-associated molecular patterns; PAMPs)
- They activate "pattern recognition receptors" (PRRs) resulting in the secretion of antimicrobial and pro-inflammatory mediators
- Antimicrobial peptides, effector molecules of innate immunity, also act as regulators of acquired immune responses, inflammation and wound repair
- Secondary bacterial colonization of HS can intensify chronic inflammation
- PRR expression in the epidermis may play a role in host defense of the skin and in chronic inflammation

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13.1 Introduction

Mild cases of hidradenitis suppurativa (HS) are characterized as recurrent isolated nodules, while severe cases of the disease with chronic inflammation may lead to scarring, functional impairment, and squamous cell carcinoma. The disease arises most commonly in any skin bearing apocrine glands and it has recently become regarded as a disorder of the follicular epitheli-

um, with follicular occlusion giving rise to clinical findings. Follicular hyperkeratosis is the initial event, leading to occlusion followed by dilatation and follicular rupture, spilling contents, including keratin and bacteria, into the surrounding dermis with resultant secondary infection. These events induce a vigorous chemotactic response with an inflammatory cellular infiltrate consisting of neutrophils, lymphocytes, and histiocytes. Abscess formation develops leading to the destruction of the pilosebaceous unit. HS and acne vulgaris together with pilonidal sinus and dissecting cellulitis all share follicular occlusion as an initial event leading to disease development. Furthermore, bacterial colonization can increase the severity of chronic inflammation both in HS and acne vulgaris.

In healthy individuals as well as in mild cases of HS, the deeper layers of the skin remain free of infection, although it is constantly exposed to injuries and challenged by environmental microorganisms. This suggests that skin itself has the ability to fight against invading microbes. This chapter will summarize recent findings concerning the role of pattern recognition receptors (PRRs), antimicrobial peptides and pro-inflammatory cytokines/chemokines in innate and acquired immune responses of the skin.

13.2 Ancient and Modern: Innate and Acquired Immunity

Innate immunity is the most ancient and common system for defense against microbial infections. It evolved a detection system, a limited set of receptors (e.g., Toll-like receptors; TLRs) against microbial signatures that remain invariant inside a class of microbes [33]. Given that epithelial cells lie at the interface between the host and the environment, the expression of TLRs on these cells provides the first line of defense against invading pathogens through the recognition of microbial motifs. Although termed PAMPs, these motifs are not restricted to distinct pathogens since they include structural molecules such as lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN), lipoarabinomannan (LAM), flagellin, zymosan or double-stranded (ds) RNA (Table 13.1), which are common to multiple species of

Table 13.1. Toll-like receptors (TLRs) expressed by keratinocytes and their ligands

Receptor	Ligand	Origin of ligand
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria
TLR2	Lipoproteins and lipopeptides	Various pathogens
	Phenol-soluble modulin	*Staphylococcus epidermidis*
	Lipoarabinomannan	Mycobacteria
	Lipoteichoic acid	Gram-positive bacteria
	Atypical lipopolysaccharide	*Leptospira interrogans* and *Porphyromonas gingivalis*
	Zymosan	Fungi
	Heat-shock protein 70	Host
TLR3	Double-stranded RNA	Viruses
TLR4	Lipopolysaccharide	Gram-negative bacteria
	Heat-shock protein 70	Host
TLR5	Diacyl lipopeptides	Mycoplasma
TLR6	Lipoteichoic acid	Gram-positive bacteria
	Zymosan	Fungi
TLR9	CpG-containing DNA	Bacteria and viruses

bacteria, yeast or viruses, respectively. In addition, a number of endogenous ligands, such as heat shock proteins or β-defensins, are also TLR ligands (Table 13.1). These endogenous molecules are also called "danger signals" released from dying or dead cells in order to trigger an inflammatory response [33].

The innate immune network of the skin consists of a range of pre-existing, rapidly mobilized host defense components including keratinocytes, neutrophils, mast cells, eosinophils, macrophages, and sebocytes. The key cellular components of the pathophysiologic processes of the skin are the keratinocytes, cells that are in a unique position between the interface of the environment and the host organism [61]. The findings that keratinocytes, which form 95% of all epidermal cells, express TLRs and are a potent source of antimicrobial and antiviral peptides and cytokines/chemokines emphasize their key role in the innate immune responses of the skin [5, 6]. Epidermal keratinocytes express, in a constitutive or inducible manner, at least 7 out of 11 known TLRs (TLR1-TLR6 and TLR9) [4, 36, 49, 59, 66]. Recognition of PAMPs by TLRs initiates quick innate immune responses such as phagocytosis, and the production of antimicrobial compounds and inflammatory mediators resulting in the killing and elimination of microorganisms. In addition, these mediators link innate and adaptive immunity, as they also function as chemoattractants for the effector cells of the acquired immune response [61].

A rapid innate immune response in the skin results in cutaneous inflammation, leading to extravasation and the homing of cutaneous lymphocyte-associated, antigen-expressing (CLA^+) memory T cells to the skin, permitting them to encounter and respond to appropriately presented antigen in the skin. The ability of T and also B cells to recombine antigen receptor genes during development provides an efficient and powerful acquired immune system with nearly unlimited specificity for antigen. Although a fundamental aspect of mammalian biology, immunologic memory is a relatively recent evolutionary event.

13.3 TLR/IL-1R Superfamily and their Signaling Pathways in the Skin

TLR/IL-1R superfamily members are characterized by the presence of a variable extracellular domain devoted to specific ligand recognition, and a highly conserved intracellular Toll-interleukin-1 (IL-1) receptor (TIR) domain that mediates signal transduction (Fig. 13.1).

13.4 Members of the TLR Family Expressed by Keratinocytes

Since Gram-positive skin-infecting bacteria such as *Staphylococcus aureus* (*S. aureus*) or *Borrelia burgdorferi* (*B. burgdorferi*) are known to be rich sources of LTA and lipoproteins, which are well-known ligands of TLR2 homodimers (Table 13.1), the abundant and constitutive expression of TLR2 in the epidermis is not surprising [36, 49, 59]. TLR2 homodimers are also involved in the recognition of lipoarabinomannan of mycobacteria and atypical lipopolysaccharides of *Leptospira* and *Porphyromonas* species [68]. TLR2 also forms heterodimer complexes with other members of the TLR family, namely with TLR1 and TLR6 [49]. These complexes are characterized by different ligand specificity, thus recognition of microorganisms through different complexes gives specificity to the immune response. The TLR2/TLR6 heterodimer is necessary for the recognition of diacyl lipopeptide, a common cell wall compound of all Gram-positive bacteria, but it is also involved in the recognition of PAMPs of fungal pathogens (Table 13.1). In contrast, TLR2/TLR1 heterodimers recognize tripalmitoylated lipopeptides (Table 13.1) [76].

TLR3 has recently been demonstrated to provide a mechanism by which dsRNA species activate the innate immune response (Table 13.1). Signaling through TLR3 leads to the expression of high levels of interferon-gamma-(IFNγ) and type-1-(Th1-) associated chemokines in a variety of cell types, suggesting that it has a key role in innate immune responses against viral infections [70].

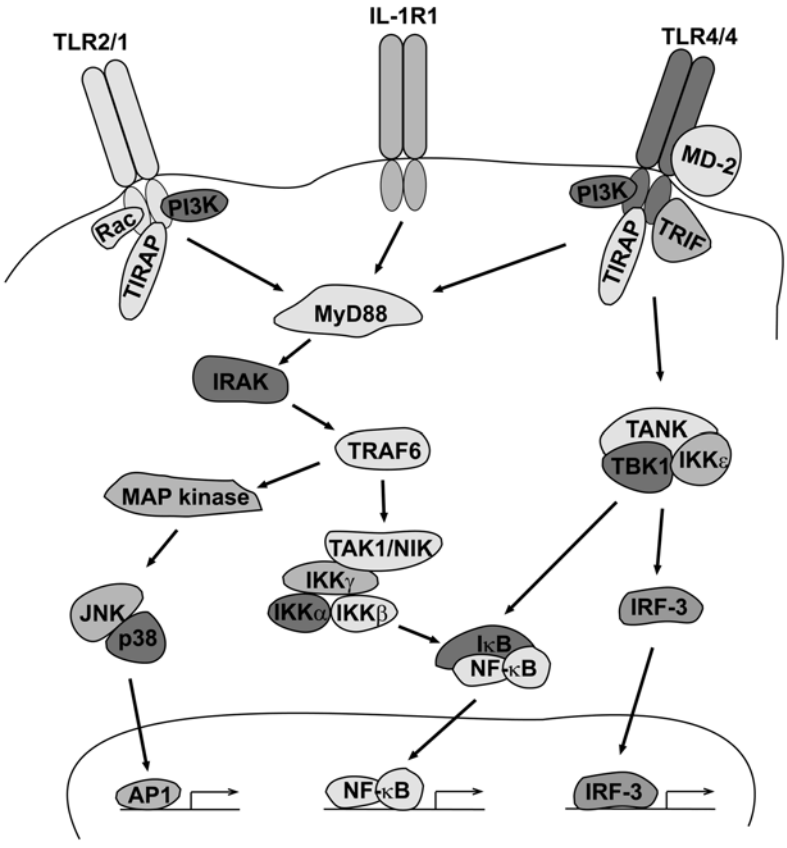

Fig. 13.1. Signal transduction pathways via TLR/IL1R. The TLR signaling pathway is highly homologous to that of the IL-1R family. After binding of an appropriate ligand, both TLRs and IL-1R interact with an adaptor protein, MyD88, through their TIR (Toll/IL-1R) domains. Upon signaling, MyD88 recruits a serine/threonine kinase, IRAK. IRAK is activated by phosphorylation and then associates with TRAF6, another adaptor protein, leading to activation of either the JNK pathway, through MAP kinase, or the NF-κB pathway, through the IKK complex. Signal transduction via TLRs and/or IL1Rs leads to the expression of antimicrobial and antiviral peptides, cytokines and chemokines. [*IKK* IκB kinase kinase, *IRAK* IL-1R-asssociated kinase, *JNK* c-Jun N-terminal kinase, *MyD88* myeloid differentiation primary-response protein, *NF-κB* nuclear factor kappa B, *TAK1* growth factor-β-activated kinase 1, *TIRAP* TIR- (TLR-IL1-R1-) associated protein, *TNF* tumor necrosis factor, *TRAF6* TNF-receptor-associated factor, *TRIF* Toll-receptor-associated activator of interferon]

The expression level of TLR4 by keratinocytes depends on the anatomical location [49]. Moreover, the expression of TLR4 (together with that of TLR2) correlates with the state of differentiation of keratinocytes [60]. Interestingly, the level of expression may also show inter-individual differences or may be inducible by mechanical injury or inflammation [59]. The recognition of Gram-negative bacteria-derived LPS requires at least two cofactor proteins in addition to TLR4. During LPS signaling, LPS first binds to CD14, which then interacts with TLR4 and initiates intracellular signal transduction. MD-2 is a protein that associates with the extracellular domain of TLR4 and enhances LPS responsiveness (Table 13.1, Fig. 13.1) [65].

TLR5 recognizes the bacterial motor protein flagellin (Table 13.1) required for the motility of microorganisms such as *B. burgdorferi*, which causes migratory erythema during the course of Lyme disease, and *Salmonella typhi*, which causes cutaneous ulceration [46]. Keratinocytes

are able to upregulate their chemokine expression in response to *B. burgdorferi*, indicating that TLR5 is functional on keratinocytes and enables them to respond to invading flagellated bacteria [16].

TLR9 senses unmethylated bacterial CpG DNA derived from many classes of bacteria during infection (Table 13.1). Its expression in the epidermis is inducible by either microbial compounds or physical trauma [12, 45]. Unlike TLR1-TLR6, TLR9 is not expressed on the cell surface but in the endoplasmic reticulum [2].

13.5 IL-1 Receptors in the Skin

IL-1 receptor type 1 (IL-1R1) can bind both IL-1α and IL-1β resulting in the initialization of MyD88-dependent signaling (see below and Fig. 13.1). The receptor, expressed on the surface of a variety of cells, mediates all known biologic activities of IL-1 by initializing a cascade of events leading to the recruitment and activation of macrophages and neutrophils, vascular dilation, fever and a proinflammatory immune response. The central role of the IL-1 system is protection against microbial colonization and infection [53].

The second receptor for IL-1, IL-1R2, also binds both IL-1α and IL-1β. By binding the functional ligands for IL-1R1, IL-1R2 serves to inhibit IL-1-mediated inflammatory responses [53].

IL-1 receptor antagonist (IL-1RA), the naturally occurring competitive inhibitor of IL-1 bioactivity, can bind only to IL-1R1 and not IL1R2. However, it does not induce signaling but reduces the IL-1-mediated inflammatory response. The IL-1RA gene is polymorphic, resulting in quantitative differences in both IL-1RA and IL-1β production. A tandem repeat sequence of 86 base pairs exists in the second intron of the IL-1RA gene. In different individuals, the number of times this sequence is repeated varies from two to six (Table 13.2). The frequency of the individual alleles varies among different ethnic or geographic populations, with the most frequent combinations being IL1RN*1 homozygotes or IL1RN*1/IL1RN*2 heterozygotes [73]. In patients with chronic inflammation, such as inflammatory bowel diseases, alopecia areata, psoriasis, lichen sclerosus or lupus erythematosus, IL1RN*2 homozygosity increases the severity of the inflammation, suggesting that persons with this allele have a more prolonged and more severe proinflammatory immune response than do persons with other IL-1RA genotypes [73]. Interestingly, the frequency of the two-repeat allele of IL-1RN is increased among patients with acne conglobata but not among those with HS. In addition, IL1RN*2 homozygosity was detected only amongst patients with severe acne conglobata, suggesting that allele 2 of the IL-1RN gene may contribute to the development of acne conglobata but not HS [38].

Table 13.2. Gene polymorphisms in the second intron of the IL-1 receptor antagonist (IL1RN)

Gene	Allele	No. of repeats[a]	Characteristics
IL1RN*1	1	4	Most common allele
IL1RN*2	2	2	Associated with prolonged inflammation
IL1RN*3	3	3	Rare
IL1RN*4	4	5	Rare
IL1RN*5	5	6	Rare

[a] Copies of the 86-base repeats

13.6 Signaling Pathways via TLR/IL-1R

13.6.1 MyD88-Dependent Signaling Pathway

Binding of specific ligand/s to TLRs initiates a signaling cascade mediated by the cytoplasmic TIR domain (Fig. 13.1). Due to the structural homology between the intracellular domains of TLRs and IL-1R, the TLR signaling pathway is highly homologous to that of the IL-1R family. Both TLRs and IL-1Rs interact with an adaptor protein MyD88, through their TIR domains (Fig. 13.1). Upon stimulation, MyD88 recruits the IL-1R-asssociated kinase (IRAK), which as-

sociates with tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), leading to the activation of at least two distinct signaling pathways, JNK and NF-κB. TLR signaling through MyD88 leads to the phosphorylation and degradation of IκB, the regulator protein of NF-κB, an event allowing the nuclear translocation of NF-κB (Fig. 13.1). In the nucleus NF-κB binds to the promoter region of genes of proinflammatory cytokines/chemokines, antimicrobial peptides, inducible enzymes, and adhesion molecules, which are important effectors or mediators of innate and adaptive immune responses [50, 81].

In keratinocytes, various microbial compounds induce a rapid TLR-dependent intracellular Ca^{2+} response. In addition, keratinocytes respond to the challenge with *S. aureus* or *Candida albicans* (*C. albicans*) with TLR2-MyD88-NF-κB-dependent induction of inducible nitric oxide synthase (iNOS), supporting the key role of the TLR-MyD88-NF-κB pathway in innate immune functions of the skin [49, 59].

13.6.2 MyD88-Independent Signaling Pathway

In addition to their common activation of the MyD88-IRAK-TRAF pathway, individual TLRs may activate different, alternative, signaling pathways. These MyD88-independent pathways involve the activation of interferon-regulatory factor-3 (IRF-3) and are utilized by several TLRs such as TLR3 and TLR4/4 (Fig. 13.1). TLR signaling pathways are therefore not identical and the specificity of some pathways may determine the pattern of gene expression, which accounts for the distinguishable biologic responses observed following the activation of specific TLRs by different classes of pathogens [69]. These specific responses may be particularly important in the epidermis, which is constantly colonized by numerous microorganisms that do not induce immune response.

13.7 Keratinocyte-Derived Effector Molecules in the Innate Immune System of the Skin

Human skin is exposed to a wide variety of pathogenic microorganisms. Despite these microbial threats, skin is highly resistant against infections. TLR-mediated signaling upon challenge with microbes and/or microbial-derived compounds induces a chemical cutaneous defense system based on the production of antimicrobial peptides and pro-inflammatory cytokines/chemokines. These keratinocyte-derived soluble factors are fundamental in the elimination of invaders and recruitment of T cells and neutrophils into the sites of skin infection.

13.8 Antimicrobial Peptides

Activation of TLRs, expressed by epidermal keratinocytes, is directly involved in the induction of antimicrobial peptides [21, 55]. This diverse family of small, mostly cationic polypeptides exerts a broad spectrum of cytotoxic activity against bacteria, fungi, parasites, and enveloped viruses. During the inflammatory processes of the skin, keratinocytes are the main cellular sources of antimicrobial peptides and their expression levels correlate with the susceptibility of the skin to infections. The local accumulation of antimicrobial proteins offers a fast and very efficient way to prevent microbes from establishing an infection. Expression of antimicrobial peptides is induced upon encounter with pathogens and during wound healing [17, 26, 44]. Activation of antimicrobial genes by PAMPs can be further increased by proinflammatory cytokines produced at sites of inflammation by either keratinocytes or other cell types [17, 26, 28, 29, 44, 64]. Most keratinocyte-derived antimicrobial peptides belong to defensin, cathelicidin or RNase gene families and are able to kill or inactivate a wide spectrum of microorganisms mainly by forming pores and permeabilizing microbial membranes.

13.9 β-Defensins

The expression of human β-defensin-1 (hBD-1), the first isolated human β-defensin, is constitutive in epidermal keratinocytes and shows antimicrobial activity against predominantly Gram-negative bacteria such as *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) [3, 20]. The constitutive expression of hBD-1 in the suprabasal layers of the epidermis suggests that it contributes to the innate resistance of the skin to Gram-negative infections.

The second human β-defensin, hBD-2, was originally isolated from the desquamated scales of psoriatic skin [26]. Several data suggest a complex role for hBD-2 in cutaneous host defense. It has a microbicidal effect against various microorganisms, such as *E. coli* and *P. aeruginosa, S. aureus* or *Streptococcus pyogenes* (*St. pyogenes*) [64], but also acts as a chemoattractant for immature dendritic cells and neutrophils, and induces the migration of memory T cells. The expression of hBD-2 in vivo is localized to the upper layer of the epidermis and the stratum corneum. hBD-2 was also found in the intercellular space indicating that the lipid "permeability" barrier of the skin contains antimicrobial substances [57]. In correlation with the localization of hBD-2 in the more differentiated suprabasal layers of epidermis, differentiation-regulated expression of hBD-2 was also demonstrated in primary keratinocytes [3, 44]. Furthermore, the abundant expression of hBD-2 in inflamed and in infected skin parallels with the finding that its expression is induced by Gram-positive (*E. coli*, *P. aeruginosa* and *Propionibacterium acnes*) and Gram-negative (*S. aureus* or *St. pyogenes*) bacteria and also by *C. albicans* in cultured keratinocytes and in reconstructed human epidermis [9, 11, 13, 26, 28, 54].

hBD-2 binds specifically to CC chemokine receptor 6 (CCR6) and mediates the chemotaxis of $CCR6^+$ cells such as dendritic cells and T lymphocytes, which have an important role in the adaptive immune response against pathogens [77, 80]. The chemotactic activity of hBD-2 for immature dendritic cells and memory T cells, however, requires much lower concentrations than its antimicrobial activity [44]. hBD-2 also induces the maturation of dendritic cells in a TLR4-dependent manner [7]. In vivo, the secretion of hBD-2 by keratinocytes activates dendritic cells, inducing their migration from the skin into local lymphoid organs, leading to the generation of the cellular immune response through the activation of antigen-specific T cells [39]. Thus, hBD-2 plays multiple roles in cutaneous host defense: (1) it provides the first line of defense against infection by acting as a "natural antibiotic" against sensitive pathogens; and (2) it plays a key role in the initiation of adaptive immune responses against infections by directing the migration of dendritic cells and/or T cells and inducing DC maturation. Taken together, hBD-2 provides a link between the innate and adaptive immune responses during skin infections.

hBD-3 has been cloned from keratinocytes and it shows a broad spectrum of antimicrobial activity against Gram-negative and Gram-positive bacteria including multi-resistant bacteria. Its expression in keratinocytes is induced by PAMPs, inflammatory mediators such as TNF-α, IL-1β, IFN-γ, and by the state of differentiation [27, 28].

Similarly to hBD-2 and -3, the production of hBD-4 in keratinocytes is inducible by inflammatory stimuli, PAMPs or differentiation [28]. Synthetic hBD-4 revealed antimicrobial activity against *P. aeruginosa* and *Staphylococcus carnosus*, implicating a role for this peptide in the innate epidermal defense against bacterial infections.

13.10 Cathelicidins

LL-37 (CAP18), the only human antimicrobial peptide that has been identified in the cathelicidin gene family, is produced in neutrophils and also induced in keratinocytes during inflammatory skin disorders [17, 43]. In vivo, LL-37 provides protection against necrotic skin infection caused by group A streptococci and it also exerts antimicrobial activity against a wide variety of Gram-positive and Gram-negative bacteria [52]. Similar to defensins, LL-37 plays multiple roles in the fight against pathogens: in addition to its antibiotic effect, it has the potential to recruit mast cells, neutrophils, mono-

cytes, and T cells to inflammation foci, and it is involved in the re-epithelialization of skin wounds [14, 29, 56].

13.11 RNase7

RNase7 exhibits high antimicrobial activity against several potentially pathogenic Gram-positive bacteria such as *S. aureus* and *Propionibacterium acnes* (*P. acnes*), Gram-negative bacteria such as *P. aeruginosa* and *E. coli* and yeast *C. albicans* [25]. Detection of RNase7 gene and protein expression in primary keratinocytes, together with its high abundance in the stratum corneum and its broad antimicrobial activity stress the role RNase7 plays in cutaneous innate immunity.

13.12 Antileukoprotease (ALP)

Antileukoprotease, a serine protease inhibitor isolated from the stratum corneum, has antiprotease activity and exhibits high antimicrobial activity against a broad range of skin-associated microorganisms such as *P. aeruginosa*, *S. aureus*, *Staphylococcus epidermidis* (*S. epidermidis*), and *C. albicans* [72]. Its constitutive expression in keratinocytes indicates that ALP actively participates in mechanisms allowing the homeostasis of bacterial and yeast colonization on human skin.

13.13 Pro-Inflammatory Chemokines

Chemokines, a superfamily of chemotactic proteins induced by contact with pathogens, regulate the recruitment of various classes of phagocytic cells, T cells and eosinophils into sites of infection. Keratinocyte-derived chemokines regulate the migration of leukocytes and neutrophils from peripheral blood vessels into inflamed skin, in a sequence of tightly controlled events involving the activation of vessel endothelium, transendothelial migration and chemotaxis [31, 32].

Skin-pathogenic microorganisms such as *S. aureus*, *B. burgdorferi* or *C. albicans* together with several PAMPs (e.g., LPS or PGN) induce the abundant expression of IL-8 [a chemokine now referred to as CXC chemokine ligand 8 (CXCL8)] in a TLR-NF-κB-pathway-dependent manner [15, 47, 49, 59, 75]. Pathogen-induced secretion of keratinocyte-derived IL-8 initiates neutrophil chemoattraction and transendothelial migration. In addition, IL-8 is selectively involved in the transendothelial migration of CLA^+ T cells, emphasizing the role of IL-8 in the homing of specific T cells to inflamed skin (Fig. 13.2). In addition to IL-8, pathogens and microbial products, such as heat-killed *S. aureus* and staphylococcal PGN, stimulate the expression of other chemokines in keratinocytes, such as RANTES/*CCL5* (regulated on activation, normal T expressed and secreted, RANTES) or MCP-1/*CCL2* (monocyte chemoattractant protein-1) [47]. RANTES-expressing keratinocytes were detected in the lesional skin of patients with atopic dermatitis and psoriasis, implying a role for RANTES in skin inflammation, possibly through the recruitment of distinct leukocyte subsets [19, 24, 63]. MCP-1/*CCL2* displays chemotactic activity to blood monocytes, memory T helper cells, and eosinophils but not to neutrophils [23, 24].

Chemokines also exert in vitro antimicrobial properties against a wide variety of microorganisms [30, 78]. Under physiological conditions 20 out of 45 known human chemokines function as potent antimicrobial factors, providing evidence for the close functional and evolutionary relationships between chemokines and antimicrobial peptides [30, 78, 79]. After challenge with microbial constituents or inflammatory signals, many of these "antimicrobial chemokines" are expressed by epidermal keratinocytes (e.g., CCL18, CCL19, CCL20, CCL25, CXCL1, CXCL10), suggesting that keratinocyte-derived chemokines are involved not only in the recruitment of professional immune cells to the sites of infection but in the direct killing of pathogens as well. Still further functional studies are needed to elucidate the exact role chemokines play in the elimination of skin-infecting pathogens.

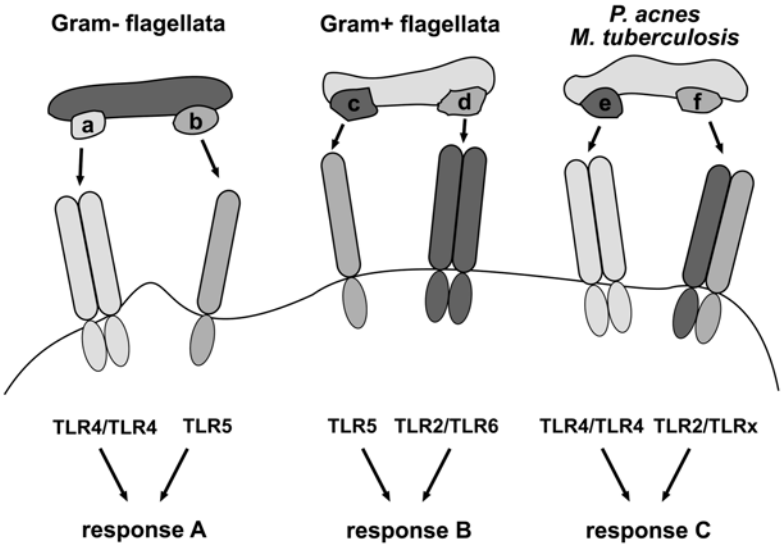

Fig. 13.2. Possible function/s of keratinocytes in hidradenitis suppurativa (*HS*). Follicular hyperkeratosis is the initial event of HS, leading to the spilling of keratin and bacteria into the surrounding dermis with resultant secondary infection. Attaching bacteria activate the production of antimicrobial peptides (e.g., hBD-2) and/or pro-inflammatory cytokines/chemokines (IL-1α, IL-1β, IL-8, IL-6, and TNF-α) in keratinocytes through the activation of TLR/IL-1R–NF-κB signaling. Keratinocyte-derived antimicrobial peptides either kill the pathogens or regulate the recruitment of memory T cells and immature dendritic cells through interaction with CCR6. Additionally, antimicrobial peptides activate immature DCs through TLR4, which leads to the initialization of acquired immune responses. Keratinocyte-derived IL-8 and pro-inflammatory cytokines activate endothelial cells allowing the transepithelial migration of neutrophils. Extravasated neutrophils follow a chemotactic gradient formed by IL-8 toward the site of infection. (*DC* Dendritic cell, *hBD-2* human β-defensin 2, *IL* interleukin, *NF-κB* nuclear factor kappa B, *TLR* Toll-like receptor, *TNF* tumor necrosis factor)

13

13.14 Pro-Inflammatory Cytokines

Upon challenge with microbial compounds keratinocytes express numerous cytokines acting as cytoprotective factors in the processes of the immune response.

In primary keratinocytes, *S. aureus*-derived PGN induces the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) [47], a cytokine essential for the survival, differentiation, and maturation of dendritic and Langerhans cells. The effects of GM-CSF on the antigen-presenting cells shift the immune response to the Th2-type. Its mitogenic effect on keratinocytes is partially responsible for epidermal hypertrophy, characteristic of chronic inflammatory skin lesions.

Skin contains a reservoir of preformed IL-1α, leading to the concept that epidermis is a shield of sequestered IL-1 surrounding the host, waiting to be released upon injury. External stimuli such as wounding, burns, and microbial infection, or internal stimuli such as local cytokine release from stimulated leukocytes can induce the release of IL-1 for local or systemic delivery. Although high levels of IL-1RA also coexist within keratinocytes, the amount of IL-1 is sufficient to overcome any potential for inhibition mediated by IL-1RA.

Both heat-killed *S. aureus* and staphylococcal PGN induce the expression of TNF-α, IL-1β, and IL-6 of primary keratinocytes [47, 51, 74]. TNF-α enhances the bactericidal effect of neutrophils and promotes the adhesion of neutrophils to endothelial cells. Thus, keratinocyte-derived TNF-α plays a crucial role in the recruitment of phagocytic cells into sites of infection. The contribution of IL-6 and TNF-α

to granulomatous skin conditions, such as cutaneous leishmaniasis, granuloma annulare, leprosy or HS, is suggested by the occurrence of these cytokines in the granulomatous reactions [1]. Upon contact with pathogens, TNF-α, IL-1α, IL-1β, and IL-6 are also implicated in the autocrine induction of antimicrobial peptide expression (e.g., β-defensins and LL-37) by keratinocytes.

13.15 TLR Recognition and the Commensal Microbiota of the Skin

The human skin is densely populated with resident microbiota, composed of commensal microorganisms such as *S. epidermidis*, *P. acnes*, *Micrococcus luteus* and/or *Malassezia furfur*. These microorganisms compete for nutrients and space, limiting each other's population size and also competing out pathogens that may attempt to colonize the skin. Despite the density of the microbiota, epidermal keratinocytes do not activate pro-inflammatory signaling cascades in response to commensal microorganisms, suggesting a complex host–microbe relationship in the epidermis. Thus, epidermal keratinocytes may need to discriminate the presence of commensals from the presence of pathogens, by mechanism/s that are not yet fully identified One possible explanation for the unresponsiveness of the skin to resident microbiota is the anatomical localization of the TLR-expressing keratinocytes. Since TLRs are expressed by the basal keratinocytes, the layer that is normally not exposed to commensal microorganisms living on the surface of the skin, the sterile and PAMP-free anatomical site may allow the constitutive expression of functional TLR complexes by keratinocytes. These cells initiate pro-inflammatory signaling only during destructive or invasive infection, breaching through the stratum corneum. Still, limitation of TLR expression to certain protected anatomical sites may not be the whole explanation, since TLRs are also expressed in the suprabasal layers of the epidermis [4, 36, 59].

Another explanation may be the induction of tolerance, a state of acquired functional unresponsiveness in keratinocytes that has been extensively studied in macrophages by the long-term presence of commensal bacteria. That commensals modulate TLR signaling is best shown by studies indicating that signaling through TLR4 or TLR2 in epithelial cells in vitro readily occurs after initial exposure to PAMPs, but not after second exposure or prolonged incubation with TLR agonists. This downregulation of signaling may occur by decreased TLR expression on the cell surface, as well as by the inhibition of TLR signaling via the expression of a non-signaling truncated form of MyD88 or by the activation of IRAK-M, a negative regulatory member of the IRAK family [18, 58, 67]. Alternatively, members of the resident flora may provide an inhibitory signal for keratinocytes to avoid inflammation in healthy individuals. However, the molecular mechanisms involved in the induction of tolerance are not entirely understood in keratinocytes and a deeper insight into these processes will most probably change our understanding of the intimate relationship between epidermal cells and the commensal microbiota.

The expression of different PRRs allows keratinocytes to identify numerous features of a single microbe simultaneously. In the presence of functional receptors, effective immune response occurs only upon recognition of specific antigen combinations. Blocking of TLR2 and/or TLR4 suppresses keratinocyte activation induced by *P. acnes* or *Mycobacterium tuberculosis*, emphasizing the role of the cooperation between different subfamilies of TLRs in the process of discrimination between commensals and pathogens [54, 61]. The "teamwork" involving TLR subfamilies enables keratinocytes to give pathogen-specific immune responses, or, in the case of skin-resident microorganisms, tolerance.

Skin commensals (e.g., *S. epidermidis* and *P. acnes*) and pathogenic bacteria both induce the expression of hBD-2 in primary keratinocytes. Still, NF-κB transcription factor is not involved in the induction by commensals, suggesting the presence of discrete signaling pathways that enable keratinocytes to discriminate between resident and pathogenic microorganisms. The in vivo biological significance of com-

mensal-induced TLR signaling is the induction of cytoprotective factors in epithelial cells. The lack of TLR-MyD88 signaling in mucosal epithelial cells (and most probably in keratinocytes) is accompanied by decreased capacity of the cells to produce cytoprotective factors such as IL-6 [62]. In the absence of these compounds, epithelial cells are highly sensitive to physical stress-induced cell death. Thus, activation of TLRs by commensal microbiota is probably critical for the protection against physical-injury-associated cell death through the induction of cell survival and/or repair during infection.

Finally, the correlation of follicular lipids with *P. acnes* in acne vulgaris, an inflammatory but not infectious disease, may indicate a new and unexpected role of skin commensal microorganisms, such as *P. acnes* and *S. epidermidis*, on human skin. Their presence may be skin protective and required for a permanent, low activation level of innate immunity in order to defend skin from acute attacks by pathogens, supporting the hypothesis of a genuine inflammatory etiology for acne and a possible, delayed, contribution by *P. acnes* [22, 54].

13.16 Skin Infections and Innate Immune Responses of the Epidermis

Normal human skin supports the growth of resident microbiota and it is colonized with a wide variety of resident microorganisms. In addition to normal flora, the skin is constantly challenged by pathogens, most of which do not cause clinical symptoms. Besides microbial adherence and virulence, environmental and local factors as well as host immunity are important components of cutaneous infections. In particular, skin becomes more susceptible to infections when the epidermal barrier function is damaged or when the keratinocyte-mediated innate immune functions are inhibited.

The pilosebaceous unit is an important site of skin infections such as acne vulgaris, folliculitis, furunculosis, and carbunculosis. A common pathogen associated with infections in the pilosebaceous unit is *P. acnes*. Although acne vulgaris is not an infectious disease, the role of *P. acnes* in the pathogenesis of acne is well documented [37, 40]. Recent results describing the expression of TLRs in the pilosebaceous unit together with the increased amount of bacteria in acne vulgaris suggest that inflammation found in acne is at least partially mediated by the TLR signaling pathways (Fig. 13.3) [40, 54].

Gram-negative organisms such as *P. aeruginosa*, *Pasteurella multocida*, *B. burgdorferi*, *Salmonella typhi*, *Bartonella* sp., *Klebsiella rhinoscleromatis* and *Vibrio vulnificus* are not typical residents of the skin's microbiota but may cause cutaneous infections [10, 71]. However, their differential recognition through various TLRs expressed on keratinocytes and the expression of antimicrobial peptides highly effective against Gram-negative bacteria play important roles in the rarity of Gram-negative skin infections.

13.17 Hidradenitis Suppurativa and the Skin Immune System

The involvement of the immune system in HS remains controversial. Immunological investigations of some patients with HS suggested no abnormalities of the immune system [15]. In contrast, other authors showed increased peripheral suppressor T cell activity [48], suggestive of a precipitating cell-mediated immune response. This is further supported by the presence of activated, HLA-DR-positive lymphocytes [8]. Although in lower numbers and preferentially located in the direct perivascular compartment, Leu-8-positive immunoregulatory lymphocytes were also present in lesions, suggestive of a loss of Leu-8 cellular antigen in lymphocytes during further migration into the dermal tissue [8]. 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 ratio over time after the initiation [8] supports the existence of a precipitating cell-mediated immune response with only a short eliciting period. Even though more recent studies have shown that dysfunctional neutrophils may also be involved in the pathogenesis of HS, no primary abnormalities of the innate or acquired immune sys-

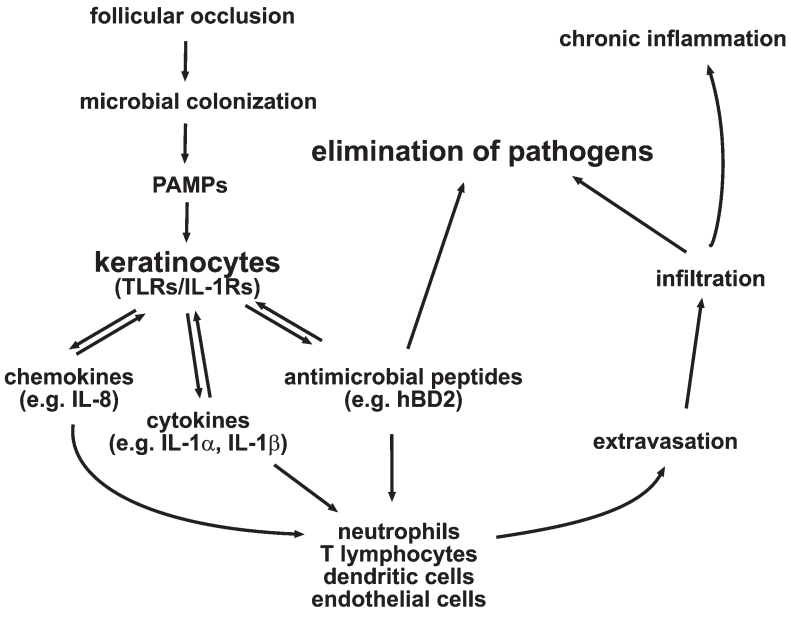

Fig. 13.3. Co-operative recognition of microbial-derived PAMPs by TLRs. Host cells use multiple TLRs for the detection of several unique features of the single microbe simultaneously. TLR4/4 and TLR5 detect LPS (*a*) and flagellin (*b*), respectively, from a flagellated Gram-negative organism (e.g., *Salmonella typhi*), whereas TLR5 and TLR2/6 detect flagellin (*b*) and diacyl-lipopeptide (*c*) of another flagellated Gram-negative organism (e.g., *Helicobacter pylori*). Keratinocytes may also recognize Hsp and lipoglycans/lipoarabinomannans (*d*) from the skin pathogens *P. acnes* and *Mycobacterium tuberculosis* via TLR4/4 and TLR2/6. (*Hsp* Heat-shock protein, *TLR* Toll-like receptor)

tem can be held to be causal in every case [8, 34, 42].

In addition, the significance of bacterial findings in HS is also controversial. It is generally accepted that the bacterial involvement is not a primary pathogenic event in HS, but rather it is likely that the chronic inflammation is due to secondary bacterial colonization [34]. 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 since numerous bacteria, such as *S. aureus* and coagulase-negative staphylococci, are most frequently isolated from lesions [35, 41]. These findings highlight a possible polymicrobial nature and predominance of anaerobic bacteria in HS, supporting the role of bacterial infections as a possible pathogenic event in HS. Microbial colonization may, in turn, trigger several events of the skin immune response, such as secretion of antimicrobial peptides and pro-inflammatory cytokines/chemokines by keratinocytes through the activation of TLR/IL-1R-NF-κB signaling (Fig. 13.3). These mediators either kill the pathogens or link innate and acquired immunity by the recruitment of effector cells, such as memory T cells and dendritic cells, to the sites of infection (Fig. 13.3). Besides, keratinocyte-derived IL-8 and pro-inflammatory cytokines activate endothelial cells, allowing the transepithelial migration of neutrophils. After extravasation neutrophils follow the chemotactic gradient formed by IL-8 toward the site of infection. Infiltration of neutrophils, dendritic cells, and T cells into the epidermis may contribute not only to the elimination of the invading pathogens but, as a result of constant activation by keratinocyte-derived mediators, to chronic inflammation as well (Fig. 13.3).

13.18 Conclusions

Increasing evidence suggests that keratinocytes not only participate in cutaneous immune responses against pathogens but may in fact play key initiation roles. Keratinocytes are able to recognize a wide variety of microorganisms through their TLRs and have evolved mechanisms to distinguish between skin commensals and pathogens. Signaling through specific TLR combinations provides selectivity and specificity to keratinocyte immune responses.

In epidermal keratinocytes, TLR-mediated signaling pathways induce the production of antimicrobial and antiviral peptides, cytokines/chemokines, and inducible enzymes. A major factor in epidermal host defense mechanisms of the epidermis is the secretion of antimicrobial peptides, as lesions of the skin characterized by low levels of antimicrobial peptides have raised susceptibility to infections. Keratinocyte-derived cytokines and chemokines are critical in the recruitment of dendritic cells, T cells, and neutrophils into sites of infection. In addition to having microbicidal functions, antimicrobial peptides can act as chemoattractants, thus providing an improved immune response against pathogens.

Taking all this into account, the epidermal keratinocytes can be regarded as potent immune cells, as they fulfill the requirements for the induction of both an innate and an adaptive immune response. These exciting discoveries extend our current understanding of the skin's innate immune functions and may give rise to future perspectives of the treatment of skin disorders such as hidradenitis suppurativa.

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Chapter 14

Quality of Life in Hidradenitis Suppurativa

14

Pierre Wolkenstein

Key points

- Quality of life is severely affected by hidradenitis suppurativa (HS)
- Suggestions for the uniform reporting of outcome variables are available and should be used
- Quality of life quantification should be made using validated instruments in all patients
- Pain should be assessed at all visits using a pain visual analog scale (VAS)

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14.1 Introduction

Hidradenitis suppurativa (HS) is a chronically relapsing skin disorder characterized by recurring inflammatory lesions leading to fistulae and sclerosis of apocrine-gland-bearing areas [3]. One or several areas are affected, including the perianal region, groin, pubis, scrotum, buttocks, inner thighs, and areola. The disease leads to painful nodules and malodorous discharge and the available treatments are only partially effective and unsatisfactory. Affected patients suffer a significant morbidity and it is self-evident that HS has a psychological impact especially upon quality of life (QoL) and mental health. In this chapter we will review these two aspects.

14.2 Concept and Measure of Quality of Life

14.2.1 Why Try to Measure Quality of Life?

Quality of life is a concept incorporating all factors that impact upon an individual's life [4]. The concept has been divided into several components, including psychological, social, and physical domains. All clinicians use an intuitive view of how much the disease is affecting their patients when taking management decisions, but patients may assess QoL differently from their doctors. The use of simple QoL measures is usually welcomed by patients who wish to express their concerns. Methods of measuring the extent and severity of a disease are based on assessment of signs and symptoms. This information does not necessarily correlate with QoL measures. It is therefore important to have two

viewpoints of a disease, the viewpoint of doctors and that of patients.

14.2.2 Reporting the Viewpoint of Patients: Methods of Measurement of Quality of Life

The techniques used to measure QoL are questionnaire based [4]. These measures either cover all ways in which patients' lives can be affected by any disease, or are more specific to diseases of systems or individual diseases. In the absence of questionnaires specific to HS, two kinds can be used: general health questionnaires and skin-disease-specific questionnaires. The questionnaires allow the calculation of either global scores, or a profile with a score for each dimension. In our experience skin-disease-specific questionnaires are more adapted than generic questionnaires to HS.

14.2.3 Reporting the Viewpoint of Physicians: Uniform Outcome Variables

The measures of the QoL must be correlated with the severity of the disease. Recently suggestions for uniform outcome variables for treatment effects in HS have been reported [7]:

1. Anatomical region involved (axilla, groin, gluteal or other region or inframammary region, left and/or right: 3 points per region involved)
2. Number and scores of lesions (abscesses, nodules, fistulas, scars; points per lesion of all regions involved: nodules/abscesses 2; fistulas 4; scars 1; others 1)
3. The longest distance between two relevant lesions, i.e., nodules and fistulas, in each region, or size if only one lesion (<5 cm 2; <10 cm 4; >10 cm 8)
4. Are all lesions clearly separated by normal skin? In each region (yes 0/no 6)

By assigning numerical scores to these variables, disease intensity can be quantified in a clinically meaning full way. A total score was calculated.

14.2.4 Practical Approach Reconciling the Viewpoints of Patients and Physicians

The evaluation of patients with HS in a referral center should include QoL questionnaires, and standardized outcome variables. Pain should be evaluated with validated instruments such as visual analog score (VAS).

14.3 Impact of HS upon Quality of Life

14.3.1 Altered Self-Reported Health: Qualitative Approach

Many dermatologists rate HS as a heart-sink condition and would agree that it ranks among the most unpleasant of skin diseases. When looking at patients' statements about their disease they emphasize that the soreness and pain are the cause of their disability. Patients suffer from embarrassment and self-consciousness caused by the frequent occurrence of boils with malodorous discharge. One study in Denmark has shown impairment of self-reported health in HS [6]: the general self-reported level of health is poorer among HS patients. The soreness, discharge, and appearance of lesions are described as problems for both work and leisure activities by 51% of all patients. In the same study, Jemec et al. [1996] found that patients with HS had lost an average of 2.7 days of work in 1 year specifically because of HS. This suggests an overall higher morbidity, as other days lost to other causes were not included in the data. The duration of 2.7 days however ranked below the average number of work days lost for all reasons per employed person (7.5 days) and even further below the average number of days lost by patients with hand eczema (4 weeks) in a comparable population. These results suggest that patients with HS fail to get appropriate recognition for the severity of their disease. Many of them seem to suffer in silence. Indeed failure to disclose the extent or even the existence of the disease may in itself increase its severity. In the absence of visible disease no support or sympathy is elicited and there is, therefore, no mitigation of suffering: the stigma attached to HS is because it

affects predominantly intimate body parts. It has connotations of socially unacceptable behavior or a lack of hygiene and is often concealed even from close relatives.

In France, in the context of a TNS Sofres survey (unpublished data), which is deemed to provide a representative sample of patients with HS, 47.2% of patients reported a medical consultation for their disease in the year preceding the interview, and 47.7% of the patients reported HS to be a relevant problem and a severe distress.

14.3.2 Measure of Quality of Life: Quantitative Approach

A quantitative approach for measuring QoL in HS was performed [2]. Questionnaires widely used in other skin diseases such as the Dermatology Life Quality Index (DLQI) questionnaire, Skindex and VQ-Dermato [1, 4, 5] were chosen. This approach allows a direct comparison of the results with those from previous studies on other skin diseases. We will discuss two studies, one already published and our unpublished data [2]. In both studies, in addition to this questionnaire, basic demographic data and aspects of the history of HS were collected: 114 patients participated in the first one [2] and 61 in the second. In the study of der Werth and Jemec [2] the recorded mean DLQI score was 8.9, higher than scores found in several other dermatological conditions such as alopecia, acne, psoriasis, Hailey–Hailey disease, vascular anomalies of face, and atopic dermatitis. In our center (unpublished data) using two other skin-disease-specific QoL questionnaires (Skindex and VQ-Dermato) [1, 5], the scores obtained were higher than those found in chronic urticaria, psoriasis, atopic dermatitis and also neurofibromatosis 1.

The impact upon QoL was correlated with the number of active lesions and with the severity of the disease. Therefore, QoL questionnaires can be used to measure the activity of the disease from the viewpoint of patients and could be used in therapeutics trials as a main criterion. In our study, three QoL questionnaires were administered and the measures obtained from each of them were strongly correlated. One can recommend using only one questionnaire and preferably one dermatological questionnaire, such as DLQI, VQ-dermato or Skindex, which seem to be more sensitive [1, 4, 5].

The DLQI score was inversely correlated with age at disease onset [2]. It was suggested that patients with late-onset disease tend to have an overall milder form of HS and a better chance of spontaneous recovery than those who develop the condition earlier in life. This is in agreement with a previous observation of the outcome of simple surgical procedures in HS, where older patients appeared to have fewer recurrences.

We used QoL questionnaires concomitantly with a VAS for pain. The QoL scores were strongly and positively correlated with the pain. Indeed, soreness and pain are the most commonly cited reason for impaired health in HS. It is self-evident that pain is one of the main burdens of patients with HS and should be taken into account as an evaluation criterion for future treatment. Patients with a long disease duration and continuous evolution were more affected than those with intermittent evolution. A pelvic location had a significantly higher impact compared to other locations. Indeed this location is associated with boils with a malodorous discharge leading to an evident physical limitation.

14.4 Impaired Quality of Life: What Conclusion?

14.4.1 Conclusion for Patients

Questionnaires of QoL are well tolerated by patients and allow one to evaluate the burden of HS and to compare it with other diseases. They demonstrated that the impact of HS is probably the greatest encountered in chronic diseases in dermatology. These results are important for recognition of the disease and the lobbying of lay groups. These questionnaires should be used when accounting for patients' viewpoints during follow-up and therapeutic trials.

14.4.2 Conclusion for Physicians

The analysis of QoL measures confirms the strong impact of HS. A subgroup of patients seems to be more affected; namely, patients with an early onset of their disease, with a long disease duration, with continuous evolution and with a predominately pelvic location. Future trials should be targeted on this subgroup. The impact upon QoL is strongly correlated with pain. Therefore, criteria of treatment evaluation should include, in addition to the standardized physician's report, the patient's viewpoint obtained with at least a dermatological QoL questionnaire and the pain VAS.

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Chapter 15

Antibiotic Therapy

15

James Leyden, Jean Revuz

Key points

- HS is not a primary infectious disease, yet antibiotics may be helpful
- Antibiotic therapy is hampered by the difficulty of realistic bacteriologic sampling
- A short course of antibiotics may stop the evolution of a nodule to an abscess if taken very early
- Empirical treatment with clindamycin and rifampicin has provided long-lasting remissions in some cases and seems to be a promising therapeutic approach

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15.1 Introduction

Antibiotic therapy is widely recommended and mentioned in all textbooks of dermatology as a prominent form of treatment of hidradenitis suppurativa (HS). Curiously, the literature reveals only a handful of primary studies on the use of antibiotics in this chronic, destructive disease. The original descriptions of chronic, recurrent abscesses in the axillary, mammary, and perineal skin and then the possible linkage to apocrine glands by Verneuil in 1854 formed a logical basis for thinking of this disease as an "infection of apocrine glands" [1]. In 1956, Pillsbury, Shelley and Kligman proposed the concept of the follicular occlusion triad and brought together acne conglobata, HS, and dissecting cellulitis of the scalp. The central event in these conditions was viewed to be follicular hyperkeratinization leading to retention of corneocytes and secondary bacterial infection [2]. This concept was strengthened by the work of Shelley and Cahn in 1955 [3]. They occluded the axillae of volunteers with impermeable plastic film and reported the subsequent formation of dermal abscesses. Their analysis was that poral occlusion of follicles led to hyperkeratosis of the distal apocrine duct, and dilatation of apocrine ducts with subsequent ductal rupture and inflammation. They described the presence of bacteria in the inflammatory infiltrate and hypothesized that bacteria trapped beneath the hyperkeratotic plug proliferated in apocrine sweat milieu with neutrophils pouring into the apocrine duct. Rupture of the duct leads to "spread of infection" and abscess formation. In this work epithelial sinus tracks were not described. In our view Shelley and Cahn more likely induced bacterial furunculosis than a chronic inflammatory process associated with epithelial sinus tract formation.

In more recent years, the concept of infection of apocrine glands has been questioned. For example, the absence or paucity of apocrine glands in lesions on the buttocks, inframammary folds, inguinal, and thigh areas argues against apocrine glands being the primary site of pathology.

Furthermore, histopathologic studies indicate that the dominant feature are epithelial-lined cysts and sinuses of follicular origin [4, 5]. The latter authors [5] proposed the term acne inversa and believe that lesions begin in terminal follicles with hyperkeratosis of the infundibulum giving rise comedo-like horny impactions with subsequent rupture of the follicular canal, and dermal inflammation with strands of epithelia extending into the dermis in an attempt to encapsulate the inflammatory reaction. Bacterial infection, when present, is a secondary, aggravating factor.

15.2 Clinical Experience

With this more modern-view pathophysiology, it may seem rational to view antibiotic therapy as useful when pathogens are recovered from furunculoid lesions or draining purulent material, provided that the sampling and bacteriological methods allow the recovery of significant, i.e., deep-seated, material and the growth of relevant species, i.e., aerobic *and* anaerobic bacteria.

Distinguishing between a non-infected, highly inflammatory process associated with nodular abscess-type lesions and a purulent discharge and true secondary infection is often not possible on clinical grounds alone. The presence of fever, cellulitis, and lymphadenopathy are helpful but are not common findings. Frequent cultures are essential for making rational decisions regarding the use of antibiotics. The need for antibiotic use driven by culture and sensitivity is even more important in view of the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in community-acquired infections.

Over the years one of us (J.J.L.) has routinely cultured HS patients (Table 15.1). All of these patients are referred by other dermatologists and have had multiple courses of systemic antibiotics and in many cases have been on continuous antibiotic therapy. The latter is rational only if one believes that the non-antimicrobial, anti-inflammatory properties of antibiotics are beneficial in HS.

The results of cultures in 150 patients with chronic disease indicate a low rate of recovery of pathogens. The most common pathogen isolated is *S. aureus* with MRSA seen in recent years. In the perineum, Gram-negative bacteria including *Escherichia coli*, *Proteus* and *Pseudomonas* species are found in a small percentage of patients. There results support the view that bacterial infection is not a primary event in HS. These findings are in agreement with Jemec et al. [6] and Lapins et al. [7]. The most frequently isolated pathogens are *S. aureus* and Gram-negative species. The studies of Jemec and Lapins circumvented the problem of collecting surface contaminants. If members of the resident cutaneous flora, e.g., coagulase-negative cocci, are recovered, they should not be considered pathogens unless the hypothesis of biofilm formation by this resident flora in a deep-seated sinus is verified (see Chap. 11). Several authors have recovered anaerobic bacteria from HS lesions [7–9]. See Chap. 11 for further information on bacterial isolates from HS lesions.

15.3 Therapy

Despite the widespread use of antibiotic therapy, there is a paucity of information in the literature. One trial found topical clindamycin superior to its vehicle while another showed no dif-

Table 15.1. Bacterial cultures in hidradenitis suppurativa

	Patients (*n*)	Cultures (*n*)	No growth (%)	*Staphylococcus aureus* (%)	*Streptococcus pyogenes* (%)	GNB (%)
Axilla	60	330	90	8	1	1
Perineum	55	255	80	10	2	8
Buttocks	20	110	90	7	0	3
Submammary	15	60	95	5	0	0

Table 15.2. Published trials of antibiotics in HS

	Design	Number of patients	Drugs	Duration of therapy (months)	Result	Reference
1	Randomized controlled trial	27	Clindamycin versus placebo	3	10% topical clindamycin superior to placebo	Clemmensen [10]
2	Randomized controlled double-blind trial	46	Topical clindamycin versus systemic tetracycline	3	No significant difference between topical clindamycin and systemic tetracycline	Jemec and Wendelboe [11]

ference between topical clindamycin and systemic tetracycline – neither worked well [10, 11] (see Table 15.2).

Short courses of antibiotics aimed at stopping an exacerbation of the disease are usually useless. In the experience of one author (J.R.) there is a subset of HS patients with mild disease who may benefit from such treatment. These patient have only a few outbreaks of one – or several – painful nodules during a year. If they start the antibiotic treatment immediately, within 1 h, of the first symptom they have a 50% chance of preventing the "normal" evolution, i.e., pain, swelling, and incision of the abscess.

Systemic clindamycin targeting anaerobic bacteria has been used in high doses, 1200 mg and 2400 mg respectively, in two patients with good improvement [8]. More recently the combination of systemic clindamycin (600 mg daily) and rifampicin (600 mg daily) was given for 10 weeks to seven patients with HS [12]. Two patients experienced diarrhea related to *Clostridium difficile*; three responded well and remained clear at 12 months. The same team has reported their experience with 14 patients – 9 women and 5 men – with long-lasting HS of mean duration 10.5 years [13]. Eight patients achieved long-lasting complete remission: 1–4 years of follow-up without recurrence. Two other patients achieved remission after minocycline was substituted for clindamycin because of diarrhea. The four other patients could not tolerate the course of treatment because of diarrhea.

One of us (J.R.) has recently confirmed these results by treating 42 HS patients (26 women, 16 men) with long-lasting disease, mean duration 11 years [14]. All were severely affected, with 21 being at stage II of Hurley's classification and 21 at stage III. All of them had more than 15 days/month of pain and 34 had permanent, painful lesions. Twenty patients had already used antibiotics, either as a short course of less than 15 days or as continuous treatment with tetracyclines. Twelve patients were followed-up by their referring physician and no data on treatment results were available. In the remaining 30 patients, 9 had a complete remission, 9 an important improvement and 11 a moderate improvement. Of these 29, 20 had had no relapse after a follow-up of 3 months to 1 year. One patient had to stop because of spontaneously healing diarrhea; eight other patients experienced mild diarrhea, recovering without stopping the treatment.

Confirmation and extension of these studies is necessary. Studies should focus on the role of infection in severely affected patients with long-lasting disease. One cannot expect such treatment to cure the disease, but it raises the hope of bringing a significant number of patients into remission. Whether other drugs, namely tetracyclines and non-steroidal anti-inflammatory drugs, can prolong a state of complete or near-complete remission will have to be explored in the future.

A note of caution about chronic antibiotic therapy, which can disrupt the normal flora of sites including the oral cavity, gastrointestinal tract and vagina; this risk needs to be weighed against the benefit seen in patients who are not colonized by pathogens.

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Chapter 16

Antiandrogens

Evelyne Drapier-Faure, Michel Faure

16

Key points

- The role of androgens in hidradenitis suppurativa (HS) is controversial
- HS may correspond to an inflammatory disease with an increased sensitivity to circulating or in situ androgens, but this view is not supported by those few cases in which there is a positive response to antiandrogens
- Further studies are needed to investigate whether HS responds to antiandrogens and to settle the controversy of whether HS can be considered as a manifestation of cutaneous hyperandrogenism

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16.1 Introduction

In 1986, two reports suggested that hidradenitis suppurativa (HS) responds to antiandrogen therapy [9, 13]. They supported the hypothesis that HS is an androgen-dependent disease. In fact, no further work exists favouring this hypothesis. Furthermore, clinical and biological investigations are really needed to elucidate the possible participation of androgens and the possibility of hyperandrogenism in HS (see Chap. 12, Endocrinology). What a so-called response to antiandrogens in HS means, and the evidence for this is really only poorly suggested, and must be discussed in terms of antiandrogen therapy.

16.2 Antiandrogens and Antiandrogen Therapies

Antiandrogens are molecules that bind the androgen receptor (AR) and act as androgen antagonists at the target cell level. Cyproterone acetate (CPA) and spironolactone are the most commonly used androgenic antagonists [3, 12].

Additional hormonal treatment of hyperandrogenism includes: (1) inhibition of the conversion of testosterone (T) into its active metabolite dihydrotestosterone (DHT) through 5α-reductase inhibition; (2) suppression of ovarian androgen production with oral contraceptives (OC); (3) elevation of sex-hormone-binding globulin (SHBG) levels through oestrogens, either natural oestradiol, (E_2, as oestrogen therapy) or ethinyloestradiol (EE, with OC), with a further decrease in plasma free androgen levels (Table 16.1).

Table 16.1. Treatments for androgenic disorders

Antiandrogens = androgenic antagonists
Cyproterone acetate
Spironolactone
Others
5α-Reductase inhibition
Finasteride
Ovarian suppression
Combination OC
Progestogens (non-androgenic)
Oestrogens
Increase of SHBG
Oestrogens
Combination OC (non-androgenic)
Weight loss
Non-hormonal
Depilation, epilation
Anti-acne (retinoids, antibiotics)

16.2.1 Cyproterone Acetate

CPA is a progestin with several antiandrogenic activities: binding to AR, inhibition of androgen metabolism and antigonadotropic activity. CPA has been used extensively in Europe for 30 years in the treatment of hirsutism. It can be given according to various regimens (usually 50 mg daily on days 1–20 of each menstrual cycle, but other regimens are possible with CPA of 50 or 100 mg) together with natural E_2 or with an OC pill. Good results may be obtained in hirsutism and also in women with severe and/or persistent acne or with androgenic alopecia. Side-effects are uncommon and the antiandrogen is well tolerated [6, 11, 17, 18].

16.2.2 Spironolactone

Spironolactone is the most generally used antiandrogen in countries where CPA has not been approved. Spironolactone binds to AR but is devoid of antigonadotropic activity. Doses needed for antiandrogenic efficacy are 75–200 mg daily depending upon the indication (acne, alopecia or hirsutism). Concomitant use of OC or a non-androgenic progestin can prevent menstruation disorders. Tolerance is good even on long-term therapy [3, 10].

16.2.3 Finasteride

Finasteride is not an antiandrogen. It does not act by blocking AR, but by inhibiting 5α-reductase, which transforms T into DHT. Finasteride inhibits the progressive hair loss in men with androgenic alopecia. It remains to be shown whether finasteride is effective in women with female-pattern hair loss. In fact, due to the possible feminization of a male fetus in the case of pregnancy whilst taking finasteride, the drug has not been approved in women [1].

16.2.4 Antiandrogenic Progestins

Other progestins with antiandrogen properties [11, 14] (antagonists at the AR levels) include chlormadinone acetate (CMA), drospirenone and dienogest. They may be used either in combination with EE [5, 8, 16] as a contraceptive OC (similarly the combination of CPA 2mg + 30 μg EE) or as antiandrogenic progestin alone (CMA for instance) according to countries where the drugs have been approved. In fact no evaluation of the effects of these progestins exists in women with hirsutism, severe acne or chronic alopecia.

16.2.5 Oral Contraceptives

Androgenic symptoms in patients with hyperandrogenism may also be minimized with OC combinations. OC may be indirectly antiandrogenic through the suppression of ovarian androgen production (antigonadotropic activity) and the oestrogen-induced elevation of SHBG. In fact, all synthetic progestins are either progesterone or testosterone derivatives. They not only bind the progesterone receptor but may also bind AR, with either agonistic or antagonistic activity. Therefore, most progestins have androgenic properties, balancing, when combined with EE, the antiandrogenic activity of EE. Therefore, OC in women with a hyperandrogenic disorder should comprise oestrogen–progestin combinations containing antiandrogenic or non-androgenic progestins. However, these OC cannot be considered as effective anti-

androgens in women with hirsutism, severe acne or chronic diffuse hair loss. Their antiandrogenic action is limited to moderate or mild acne, in association with other anti-acne therapies [3, 14, 15].

16.3 Antiandrogens in HS

There are only three reports suggesting a possible role for antiandrogens in the management of HS.

16.3.1 Cyproterone Acetate

In 1986 Mortimer et al. [9] published the first and only study of the effects of CPA in women with HS. This was a double-blind controlled cross-over trial of EE 50 μg /CPA 50 mg compared to an ordinary OC in combination with EE 50 μg/norgestrel 500 μg, in 24 female patients for 12 cycles. They reported substantial improvement in disease activity with both treatments. In fact, only 18 patients out of 24 completed the trial and only 12 patients improved, while 4 deteriorated. No clinically significant differences between the two regimens were noted. Indeed, objective assessments provided insufficient evidence for improvement. "Accurate" assessments could only be made with knowledge of the frequency and severity of attacks of the disease, as judged by the patients themselves [9].

The fact that no difference was noted between the two groups does not favour a role for CPA as an antiandrogen in HS. The combination used in the control group was an OC with an androgenic progestin. In hirsutism, which is a major skin hyperandrogenic condition, and in severe acne, this kind of combination with either 50 μg or 35 μg EE is not effective, while 50 mg CPA daily is. If some improvement in HS could be noted in 12 patients out of the initial 24, whichever combination was used, this cannot be related to the antiandrogenicity of CPA. Rather, it may reflect the indirect antiandrogenicity of EE, decreased ovarian androgen production and increased SHBG synthesis, as evidenced by the variations in plasma testosterone, SHBG and T/SHBG ratio (free androgen index) that were noted.

Also in 1986, Sawers et al. [13] reported the analysis of four women with HS who received CPA in combination with EE according to the then classic reversed sequential regimen of Hammerstein, namely 100 mg CPA per day for 10 days and 50 μg EE per day for 21 days. This was a classic antiandrogenic regimen used to treat hirsutism. All four patients were reported to exhibit objective clinical improvement and to report a subjective impression of improvement after only one to two cycles of treatment. Three patients experienced a worsening of the symptoms when CPA was reduced. In fact, it is questionable whether these women, or at least two of them, were really suffering from HS and not from acne. Furthermore this was merely an uncontrolled study, an open report of only four cases of "mild" HS under antiandrogen and oestrogen therapy.

In fact there are presently no studies to suggest a role for CPA as an antiandrogen in the management of HS.

16.3.2 Spironolactone

No study exists on the effects of spironolactone as an antiandrogen in women with HS. However, Cunliffe noted in 1989 that some clinical benefit had been obtained in an uncontrolled study with spironolactone 200 mg daily in about half of patients [2].

16.4 Finasteride

Two patients were reported in 1999 by Farrell et al. [4] to have a good response to finasteride (5 mg/day), a dose five times higher than that used in male alopecia. A 56-year-old man with a 10-year past history of HS reported significant improvement in his symptoms as early as the 4th week of treatment. A 55-year-old postmenopausal woman with a history of HS since adolescence and a previous absence of response to CPA received finasteride 5 mg/day. After 3 months she reported an improvement of her lesions without any significant adverse effects.

Since then, seven patients of both sexes have been treated with finasteride 5 mg/day in an open study with follow-up periods ranging from 8 months to 2 years [7]. Three patients had complete healing of lesions and six patients were said to improve significantly. In fact, double-blind placebo-controlled studies are needed to clarify this situation.

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Chapter 17

Oral Retinoids for Hidradenitis Suppurativa

17

Jurr Boer

Key points

- Therapy with isotretinoin for patients with HS has only limited therapeutic benefit
- There are claims that etretinate and acitretin are superior to isotretinoin. These data, however, wait confirmation in larger patient series

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17.1 Introduction

Isotretinoin is well recognized as the most successful therapy for acne vulgaris. It is traditionally thought that hidradenitis suppurativa (HS) and acne are closely related, and because of this isotretinoin has also been tested in HS, as have the related compounds etretinate and acitretin.

17.2 Isotretinoin

17.2.1 Mechanism of Action [1, 2]

The mechanism of action of isotretinoin in HS is unknown. In HS, the initial event is believed to be poral occlusion. Retinoids can normalize follicular cornification, although etretinate and acitretin have a clearly greater effect than isotretinoin in disorders of keratinization [3]. It has also been shown that isotretinoin can reduce ductal hypercornification [4]. Isotretinoin possesses anti-inflammatory effects, reduces the chemotaxis of polymorphonuclear leucocytes and has been reported to enhance immune function [5, 6]. These properties may be of benefit in the treatment of HS. The main effect of isotretinoin is to decrease of the size and secretions of the sebaceous glands.

However, in contrast to what happens in acne, the size of sebaceous glands is not increased in HS. Isotretinoin also reduces the ductal population of *Propionibacterium acnes*, and although this has a very important effect on acne pathogenesis, it does not appear to be useful for the treatment of HS, because *Propionibacterium acnes* has not been cultured in HS lesions. Isotretinoin does not affect the size of apocrine glands.

17.2.2 Clinical Experience

17.2.2.1 Isotretinoin Monotherapy for HS

Isotretinoin monotherapy for patients with HS has limited therapeutic benefit. This is both the general overall impression of many experts as well as the outcome of a study in which a large case series of 68 patients were followed over a period of almost 9 years [7–12]. The results of case reports and studies with case series are summarized in Table 17.1.

All studies lack control groups with antibiotics or other agents as a comparison, so no statement as to relative efficacy can be made. However, in all the referred case studies many patients did not respond to oral antibiotics or surgery, or relapsed after such treatment.

It is well known that acne patients with epithelial sinus tracts with recurrent inflammation respond poorly to isotretinoin and are in fact most of the isotretinoin "failures," at a high cumulative dose of isotretinoin as well [6, 13, 14]. These lesions are identical to those found in the axillae and groin in patients with HS [13, 14].

Shalita and co-workers [13] suggested that in early cases in which only inflammatory furunculoid lesions exist and undermining sinus tracts have not yet developed, isotretinoin alone can produce complete suppression and prolonged remission. Boer and van Gemert [12] also found some indication that the response of HS to isotretinoin is more successful in the milder (furunculoid, papulo-pustular lesions) cases. It may be that treatment with isotretinoin at the earliest stages of HS corrects the follicular abnormality that is the root of this chronic disease [15].

17.2.3 Isotretinoin Therapy in Patients with Acne and Coexistent HS

It is well known that acne and HS can occur in the same person. In addition to the coexistence of acne and HS, there are the so-called acne triad (acne conglobata, HS and perifolliculitis capitis abscedens et suffodiens) and acne tetrad (original acne triad and pilonidal sinus) conditions [16]. This clinical overlap of acne and HS has led to the inclusion of inhomogeneous patients in the treatment groups. It concerns two possible different types of HS; firstly the disease that only affects the inguinal folds and the axil-

Table 17.1. Reported results of isotretinoin therapy for hidradenitis suppurativa (HS)

Author (s)	No. of patients	Dose (mg/kg per day)	Duration of treatment (months)	Follow-up (months)	Duration of HS (years)	Severity of HS	No. of patients with an (almost) clear score	
							At the end of treatment	At the end of follow-up
Jones et al. [7]	3	1.0	4	–	20–30	Severe	0 (0%)	–
Dicken et al. [8]	8	0.71–1.2	4	2–6	5–35	Severe	4 (50%)	1 (12.5%)
Norris and Cunliffe [9]	6	1.0	4	2	many years	Severe	0 (0%)	–
Brown et al. [10]	1	1.0	4	4	3	Severe	1 (100%)	1 (100%)
Mengesha et al. [11]	1	1.0	8	12	1	Severe	0 (0%)	–
Boer and van Gemert [12]	68	0.5–0.81	4–6	6–107	1–30	Mild to severe	16 (23.5%)	11 (16.2%)

Table 17.2. Reported results of isotretinoin treatment of patients with acne and coexisting HS

Author (s)	No. of patients	Dose (mg/kg per day)	Duration of treatment (months)	Improvement of HS	Recurrence
Jones et al. [18]	1	0.1–1.0	4	No change	–
Plewig et al. [19]	Un-specified	1.0–2.0	3	To a certain extent	–
Peck et al. [20]	2	High, no precise data	No data	Improvement	–
Shalita et al. [13]	Uns-pecified	0.5–1.0	4–5	Only suppressed furunculoid lesions. No change in sinus tracts	–
Harms [21]	2	0.5–1.0	6	Improvement	–
Harms [2]	5	No data	No data	Considerable improve-ment in 4 out of 5 patients	No
Libow and Friar [22]	1	0.2–1.0	9	Quiescent	No

lae ("Verneuil's disease"), and secondly inguinal and axillary involvement in patients with acne affecting the face and back [2, 13, 17]. The last disease has also been called acne ectopica and acne tetrad.

It has been suggested that patients of these two categories would respond to isotretinoin in different ways [2, 13, 14, 17]. The data are summarized in Table 17.2.

Harms [2] treated eight patients suffering from HS, of whom five had concurrent acne of the face and three did not. Four out of five patients with the combination of acne and HS improved considerably under treatment with isotretinoin and did not suffer any recurrence. The three patients who had only inguinal involvement did not improve (data about the doses, duration of isotretinoin course and follow-up were not mentioned). It was concluded that patients with lesions only in inverse areas (axillae, groin) should not be treated with isotretinoin and that there may be patients with HS who respond very well to isotretinoin, namely those with a combination of acne and additional HS [2, 17].

Other authors [13, 14] found that patients with sinus tracts in the areas of acne with coexisting HS of the axillae and groin were often isotretinoin "failures," in that isotretinoin therapy did not always totally suppress this type of lesion. The conclusion of the authors was that sinus tracts require surgical removal [13, 14].

In several initial trials of isotretinoin in acne, the investigators often included some patients with HS in addition to their severe acne. Jones, Blanc, and Cunliffe reported one case who failed to respond after a 4-month course on an unspecified dose of between 0.1 and 1.0 mg/kg per day [18]. Plewig and colleagues treated an unspecified number of patients with acne tetrad who responded to a certain extent [19]. Peck et al. included two patients with HS in the groin and axilla in addition to their cystic acne, who showed improvement of the HS after the cystic acne had begun to improve and when the dosage had been further increased above the level required to improve their acne (the actual doses used were high but not specified) [20]. Harms described in a case series of 56 patients with nodulocystic acne including two patients with ano-inguinal lesions which only improved on isotretinoin at a dosage of 0.5–1.0 mg/kg per day for 6 months [21]. Libow and Friar reported effective treatment of a patient with arthropathy with associated acne triad condition with isotretinoin [22]. A patient has been described with arthropathy associated with cystic acne, HS (in this case papulo-pustules and cysts in-

volving the genital and inguinal areas, no sinus tracts), and perifolliculitis capitis abscedens et suffodiens who showed a dramatic response to isotretinoin (1.0 mg/kg per day) for 6 months, followed by isotretinoin (0.5 mg/kg per day every other day) for another 3 months before being discontinued. At the completion of 6 months of therapy, his cutaneous disease was quiescent and there was no recurrence of either joint or cutaneous disease (a follow-up period was not mentioned).

So, the results of these case reports [2, 13, 18–22] are at best equivocal compared to the excellent results in acne treatment. In the same patients the acne seemed to clear completely or was much improved, while in most case reports the HS lesions obviously remained and showed only a limited response. A follow-up period was never mentioned. A (partial) response of HS lesions to isotretinoin was also more slow to develop than the response to acne. Moreover, isotretinoin has a very poor effect on sinus tracts, whether located in the same area as the acne or in the axillae and groin [13, 14, 16, 23].

17.2.4 Isotretinoin in the Pre- and Postoperative Phase

The use of oral isotretinoin has been recommended by Plewig and co-workers during the weeks or months before surgery and even postoperatively [16, 24]. The drug has anti-inflammatory activity and may drastically reduce suppuration and edema [24]. It also reduces the volume of the sebaceous glands and alternates the pattern of keratinization within the follicle [25]. It has been suggested that in this way the area involved by HS lesions can be significantly reduced [25, 26], although isotretinoin by itself is insufficient to stop the disease [16, 24].

In various German trials, patients were treated with an unspecified dose of between 0.2 and 2.0 mg/kg per day for the 2–4 months before surgical intervention until some days postoperatively and, if indicated, in combination with glucocorticosteroids for 2–3 weeks at a dose of 0.2–1.0 mg/kg per day and systemic antibiotics [24–26]. Lentner, Rübben and Wienert then reported on 28 patients with HS who responded only poorly to oral antibiotics and isotretinoin (dose were not mentioned) [27]. The authors did not observe preoperative "conditioning" of the HS regions and in their case series they did not recognize any minimalization of the areas involved by the HS lesions. No controlled trials are available to assess the claims of the usefulness of this pre- and postoperative treatment with oral isotretinoin.

17.2.5 Isotretinoin in Combination Treatment of HS

One author reported on a patient with Crohn's disease and HS who showed a satisfactory outcome following treatment with azathioprine (150 mg/day) and methylprednisolone (16 mg/day) combined with isotretinoin (0.7 mg/kg per day) and periodic administration of antibiotics [28]. Another report details a patient with multiple pustular and cystic lesions located on swollen and red labia majora. She was successfully treated with prednisolone and erythromycin for months and then long-term isotretinoin (mostly 1.0 mg/kg per day) for 15 months, and no significant relapse of the so-called vulval apocrine acne occurred during a follow-up period of 10 months [29].

17.2.6 Side-Effects

The side-effects of isotretinoin are very numerous [2, 30–32]. In the studies mentioned, no serious side-effects are reported. In patients who are treated with isotretinoin (mostly for 16 weeks), liver function tests and determination of lipid profiles have to be performed at baseline and on one occasion after 4 weeks [31]. Teratogenicity is by far the most serious of all the side-effects of retinoids and requires responsible prescribing by physicians and reliable patients [31, 32]. Women of child-bearing age must not start therapy until a negative pregnancy test result within 1 week before starting therapy has been obtained. Adequate contraception, i.e., two reliable forms of birth control, must be used before and during oral isotretinoin therapy, as well as for 6 weeks post-therapy. Therapy should start

on the second or third day after the onset of the next normal menstrual period. It is strongly recommended that prescribers write prescriptions for no more than a 1-month supply at a time and that patients undergo monthly pregnancy testing [32].

17.3 Etretinate and Acitretin

17.3.1 Mechanism of Action

There is a broad base of clinical experience with etretinate and acitretin in the treatment of chronic keratinizing disorders [33]. If ductal hyperkeratinization is crucial in the pathogenesis of HS, etretinate and acitretin could be good alternatives to isotretinoin, because these drugs have a clearly greater effect on hyperkeratinization [3]. In addition, etretinate and acitretin show considerable immunomodulatory and anti-inflammatory effects [33]. Acitretin, the active retinoid metabolite, has generally replaced etretinate in retinoid therapy, certainly in psoriasis because of its more favorable pharmacokinetic profile, including a significantly shorter half-life.

17.3.2 Clinical Experience: Etretinate and Acitretin for HS

Etretinate and acitretin were of great benefit in all ten patients with HS, as described in five case reports [33–38]. In 1984 Stewart [34] was the first to report on HS treatment with etretinate in a study of six patients; four other case reports followed in the period from 1988 until 2002 [35–38]. The data are summarized in Table 17.3.

Overall, eight patients were treated with etretinate at a dose of 0.35–1.0 mg/kg per day [34, 36, 37] and two patients with acitretin at a dose of 0.5–1.0 mg/kg per day [35, 38]. Six out of ten patients were on isotretinoin (0.8–2 mg/kg per day) before starting etretinate and acitretin, of whom two were in Stewart's series [34] and their dosage is not mentioned. The results were unsatisfactory in all cases. The doses of isotretinoin were usually high, i.e., two full courses for 4 months of isotretinoin at a dose of 1.4 and 2.0 mg/kg per day, respectively [38]; two courses at a dose of 0.8 mg/kg per day for 4 and 3 months, respectively [36]; two full courses for 5 months at a dose of 2 mg/kg per day [35], and in one patient a 4-month course of isotretinoin (1 mg/kg per day), which cleared the patient's acne conglobata but was singularly unhelpful for his HS lesions [37]. Stewart [34] treated his six patients with ongoing doses of etretinate and they were observed over periods of 6–39 months. After 3 months of treatment, three patients showed good clearing of disease (50%–75%) and after 12 months of treatment all patients eventually had an excellent response. The criteria for clearing in the HS patients were: disappearance of sinuses and cessation of discharge. Two patients were taken off etretinate, and it took 4 months for them to begin to show signs of disease recurrence (increasing discharge and formation of the old sinus tracts). Hogan and Light [35] treated a 24-year-old women with a 6-month course of acitretin at a dosage of 0.5 mg/kg per day. After 2 months of treatment with acitretin a 50% decrease in induration of the axillae was noted. After 4 months of treatment there was no longer any induration or abscess formation in her axillae. Her HS remained in remission until 11 months after discontinuation of acitretin. Therapy was reinstituted with success [35].

Vahlquist and Griffiths [36] treated a 47-year-old man with etretinate (0.7 mg/kg per day). Within a few weeks the lesions had become less painful. After a treatment period of 11 months, the patient was essentially free of active lesions and the etretinate therapy was discontinued. Although scarring was still a problem, the patient had no longer pain. A minor relapse was recorded 1 year after stopping etretinate and this was successfully controlled by a short course of oral antibiotics [36]. Chow and Mortimer [37] treated a 31-year-old man with etretinate (0.5 mg/kg per day) for 9 months, the first 3 months together with erythromycin 1 g daily. Within 2 months, he was showing signs of improvement, with less pain, less discharge, and a decrease in the number of acute exacerbations. After 3 months there was no sign of disease activity, although linear fibrotic bands of scarring remained. Disease was still in remis-

Table 17.3. Reported results of etretinate/acitretin therapy for hidradenitis suppurativa (HS)

Author (s)	No. of patients, sex, age (in years)	Region	Retinoid dose (mg/kg per day)	Duration of treatment (months)	Follow-up (months)	Duration of HS (years)	Improvement[a]	
							At the end of treatment	At the end of follow-up
Stewart [34]	3F: 34, 36, 64 3M: 31, 32, 55	Mixed	Etretinate 0.35–1.1	3–39	3–39	No data	Clear[b]	Clear with ongoing treatment
Hogan and Light [35] 0.5	1F: 24 6	Mixed At least 11 months	Acitretin 10	clear	Mild flare 11 months; clear with acitretin			
Vahlquist and Griffiths [36]	1M: 47	Buttocks	Etretinate 0.7	11	Years	12	clear	Minor flare 12 months; clear with antibiotics
Chow and Mortimer [37]	1M: 31	Mixed	Etretinate 0.5	12	3	5	clear	Clear
Scheman [38] 0.6–0.9	1M: 41 12	Groin 12	Acitretin No data	clear	Clear with ongoing treatment			

[a] Clear defined as no disease activity; fibrotic bands and scarring remain
[b] Two patients discontinued etretinate after 3 months, for reasons not mentioned

sion 3 months after stopping etretinate [37]. Scheman [38] treated a 41-year-old man, who presented with severe nodulocystic facial acne and HS on the inguinal folds, with acitretin (0.6 mg/kg per day). After 2 months, the patient's HS was completely controlled, and his very severe acne improved to only a few inflamed nondraining facial cysts. With a dosage of acitretin of 0.9 mg/kg per day the patient was completely free of inflammatory lesions on his face and groin. After 4 months on this dosage, however, alopecia and unacceptable joint pain developed. After 1 month off acitretin, the patient's side-effects resolved. Treatment was resumed back at a dose of 0.6 mg/kg per day, with results similar to those when the patient was previously on this dosage. After 5 months of therapy, improvement continued to be satisfactory [38].

It is of concern that no controlled studies have been published. Nevertheless, there seem to be some striking points in these case studies. All patients (n=10) treated with etretinate or acitretin at a dose of 0.35–1.1 mg/kg per day responded excellently. All patients were essentially free of active lesions [36], and were completely free of inflammatory cysts [38] and sinus tracts [34]; any induration and abscess formation disappeared [35–37], although linear fibrotic bands of scarring remained [36, 37]. These excellent responses were obviously not obtained by earlier courses with isotretinoin in the same patients. In addition, the decrease of disease activity seemed to start after approximately 2 months of treatment. However, in a panel discussion Cunliffe stated that their group treated three or four patients with etretinate without too much success (unpublished observations). The treatment with etretinate was stopped after 6 or 8 months [39].

17.3.3 Side-Effects

Etretinate is a prodrug of acitretin with a molecular weight about 10% greater than that of acitretin, with the consequence that the daily dose, usually 30–75 mg etretinate, corresponds to 20–50 mg acitretin. In the early 1990s, many patients had been treated with either etretinate or isotretinoin for as many as 15 years and had not developed any signs of severe toxicity [39]. Acitretin has been established as a safe, effective treatment for psoriasis [39–41]. Retinoids, including etretinate and acitretin, are potent teratogens, leading to strict requirements for pregnancy prevention during and after their use [39–41]. Etretinate can be prescribed for male patients or postmenopausal female patients [41]. Premenopausal fertile woman should not be treated with etretinate but can be considered for acitretin therapy providing they use adequate contraception during therapy and for 24 months [39, 41] or even 36 months [40] after discontinuation. In fertile female patients it is also suggested to do a pre-treatment pregnancy test and repeated pregnancy tests every month of therapy [41].

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Chapter 18

Immunosuppressive Therapy in Hidradenitis Suppurativa

18

Hanne Nybæk, Gregor B.E. Jemec

Key points

- Immunosuppression is a possible therapeutic strategy in the treatment of hidradenitis suppurativa (HS)
- Immunosuppressive or anti-inflammatory drugs are generally safe in HS
- The use of immunosuppression in the absence of bacterial infection often brings rapid relief to patients
- Immunosuppressive drugs can be used to control flares, and prepare the patient for surgery, for example
- Longer term immunosuppression may help the patient gain better control of their disease for a period
- Immunosuppressive therapy alone is unlikely to be curative

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18.1 Introduction

Hidradenitis suppurativa (HS) is an inflammatory skin disease. The clinical presentation and historical concept of the disease have traditionally been interpreted to indicate that bacteria have a pathogenic role, but specific microbiological investigations have suggested that the role of bacteria is generally not that of a simple infection. Routine cultures are more often than not found to be sterile, and recognized pathogens such as *Staphylococcus aureus* can be found mainly in rapidly evolving lesions [1, 2]. Heavy bacterial overgrowth of known pathogens is therefore not a main feature of the disease, and the pathogenic role of bacteria may be an immunological one. Bacteria may only be the antigen that starts an immunological disease. Similar mechanisms have been described in guttate psoriasis and atopic dermatitis. In acne, bacterial antigens have also been shown to elicit an immunological response, suggesting a similar mechanism.

Similarly scarring is a prominent feature of more advanced disease [3]. Whereas scarring is currently not amenable to medical therapy, preventive medical therapy may be of clinical interest. Since the primary pathogenic event in HS is not known, treatment directed at minimizing scar formation is of independent interest to all involved. Immunosuppressive therapy has a potential in reducing the inflammatory phase of the disease, which may result in subsequent scar formation. Accepting the possibility of such a mechanism, a different range of therapeutic options becomes available to the dermatologist.

Table 18.1. Immunosupressive treatment of HS

Drug	Author	Number of patients	Location	Dosage and duration	Outcome
Ciclosporin	Gupta et al. [8]	1 (male, 60 years)		6 mg/kg for 6 weeks	Moderate response
	Buckley and Rogers [9]	1		4.5 mg/kg	Good response
	Rose et al. [5]	2 a. Female 38 years[a] b. Male 31 years	a. Groin b. Axillae and groin	a. 4 mg/kg (3 months) then tapered to 2 mg/kg for continuous therapy b. 3 mg/kg for 3 months	a. Continuous therapy with good effect b. Remission for 4 months after 3 months of treatment
Dapson	Hofer and Itin [11]	5	Axillae and groin	25–100 mg/day	Effect within 2–4 weeks, described as very good by 2 and good by 3 patients
Methotrexate	Jemec [12]	3	Axillae and groin	12.5–15 mg per week for 6 weeks to 6 months	No effect on primary lesions or recurrence rates, but slight weakening of flare intensity

[a] Patients previously treated with corticosteroids.

18.2 What Can We Achieve With Therapy?

The obvious goal of therapy in HS is to heal existing lesions and prevent the development of new lesions. This is potentially possible in early lesions (Hurley stage I), where scarring does not dominate the clinical picture, although this form of treatment is more likely to alleviate symptoms than to cure patients. Therapy may furthermore not influence established fibrosis, although intralesional steroids, for example, are commonly used to treat hypertrophic scars.

Immunosuppression however has immediate benefits for patients. The main symptom for most patients with HS is pain, which in turn is due to inflammation. By offering patients immunosuppressive therapies inflammation is reduced and pain alleviated. Immunosuppressive therapy therefore has both immediate and potential long-term benefits for patients.

18.3 Immunosuppressive Therapies

A limited body of data exists to describe the therapeutic experience of using immunosuppressants in HS. It is not clear whether it is the immunosuppressive or the anti-inflammatory effect of these drugs which is the stronger when used for HS, although it may be speculated that long-term results stem from immunosuppression rather than anti-inflammatory therapy. The therapies are however at best described through small case series, and the evidence base of these therapies therefore needs to be expanded. Dose-finding or testing observations are both necessary and interesting, and any positive findings have to be confirmed in actual randomized controlled trials (see Table 18.1).

18.3.1 Prednisolone and Other Corticosteroids

Early studies of adrenocorticotrophic hormone (ACTH) and corticosteroids suggested that general immunosuppression was beneficial to the well-being of HS patients [4]. These studies however do not conform to current requirements for evidence as they are anecdotal rather than randomized and controlled. Relief is however regularly offered to patients with flares of HS by treating with prednisolone, either as monotherapy or in combination with other therapies. In this manner systemic corticosteroids may be used in a manner analogous to their use in acne fulminans. Usually doses of 0.5–0.7 mg/kg are sufficient to achieve control of the inflammation. Initial doses can then be tapered over weeks to control the disease. However, in some cases tapering is not possible due to rapid flares and alternative therapies must therefore be instituted. The patients reported by Rose et al. [5] are examples of such cases. Systemic corticosteroids are therefore often used in conjunction with other therapies such as antibiotics [6, 7].

Careful swabbing and biochemical control are necessary to identify ongoing clinically significant infections when prednisolone therapy is instituted. Similarly patients must be informed of possible side-effects of the treatment.

Intralesional steroids are also an important tool for HS management, although their use is again unsupported by formal studies. Intralesional steroids are most often used to treat recalcitrant nodules in HS (see Chap. 21). Triamcinolone (10 mg/ml) is the most commonly used drug, but other drugs may be as efficient. The effect of the injection occurs after a few days, either as the disappearance of the lesion, or spontaneous rupture. Pain is generally reduced significantly in a short space of time. The long-term effect of using intralesional corticosteroids is not known. In our experience complications, with for example superinfection, are rare, and can be monitored through more aggressive microbiological sampling with regular swabs from lesions that do not react in the described manner but persist or develop in spite of treatment.

18.3.2 Ciclosporin

Single cases have been presented showing the beneficial effects of ciclosporin (CsA) in the management of HS [8, 9]. CsA has been used successfully where patients' responses to systemic corticosteroids were found to be unsatisfactory because of rapid relapses [5]. One case found that a 4-month remission was induced by CsA therapy, and that subsequent flares were milder, but CsA has also been used as a low-dose, long-term suppressive therapy.

A beneficial effect of CsA would be in accordance with the described early changes of HS, where a perifollicular lymphocytic infiltrate has been found [10]. In other diseases the use of CsA has furthermore been characterized by a rapid onset of effect, which may be of particular interest to HS patients because of the associated pain reduction. No long-term results (years) or larger case series have been reported.

18.3.3 Dapsone

This traditional drug has been widely used in the treatment of acne conglobata. A case series has been published suggesting its efficacy in HS as well [11]. Potentially this drug may have antibacterial effects as well, but the main effect is immunosuppressive. Any effect in HS should be suspected as being due to general immunosuppression rather than a specific effect on neutrophilic granulocytes, which are not common in HS lesions.

18.3.4 Methotrexate

The histological similarities and co-occurrence of HS and Crohn's disease have led to speculation that treatments used for Crohn's disease may have a role in the management of HS as well. This is further supported by the beneficial effects of biologics in HS (see Chap. 20). Methotrexate is another drug used in Crohn's disease that has been evaluated in a small open case series. The results were variable, and although individual patients experienced some relief from symptoms, an overall evaluation suggested only

a weak effect on the severity of HS flares and no apparent effect on the recurrence rate [12]. It is possible that a higher dose of methotrexate than the one examined could influence the results positively.

18.4 Hidradenitis Suppurativa as a Side-Effect of Immunosuppressive Drugs

HS has also been described as a side-effect of immunosuppression associated with rapamycin (Sirolimus®) treatment [13]. This drug has been reported to be associated with acne-like and other follicular inflammation in renal transplant patients. The study was carried out with stringent dermatological evaluation of patients, and an incorrect diagnosis of HS is therefore relatively unlikely. Specific immunosuppressive mechanisms may therefore play a role and not all immunosuppressants may be suitable for use in HS. In addition, bacterial infections may simulate HS to non-dermatologists and cause additional confusion.

18.5 Practical Use of Immunosuppressive Therapy

Immunosuppressive therapy can be used at all stages of the disease for the benefit of the patient. Essentially it may be directed at two different aspects of the disease: disease progression and flares.

When used to treat disease progression it is a long-term therapy aimed at controlling the inflammation-induced fibrosis of the tissue, and helping the patient to take more control of their disease. The treatment should be continued for at least 3 months with monitoring of the effect as well as possible side-effects specific to the drug chosen. Very often patients have experienced a relentless progression of their disease and are therefore highly encouraged by the alleviation provided by these drugs. The clinical impression is therefore generally favorable, although proper randomized controlled trials are lacking. By viewing HS as any other inflammatory skin disease, parallel conclusions may however be drawn about the benefits of such a therapeutic strategy. It may be speculated that long-term immunosuppression and a subsequent reduction of the inflammatory processes may stop or delay the subsequent fibrosis which forms a major factor in the perpetuation of this disease.

In contrast, treatment of flares is a short-term treatment, in which the immunosuppression is aimed at easing the patients' problems, but most often it is used in conjunction with other therapies that may be perceived as being more curative. Particularly in the early stages of the disease immunosuppression may help gain sufficient control of a lesion to allow more curative surgery, as this is made easier if the tissue is not highly inflamed at the time of the operation. Intralesional therapy may be used to achieve this (see Chap. 21). Similarly, immunosuppression at later stages may be combined with, for example, antibiotics to treat the combined effects of long-standing HS and superinfection more effectively.

Just as for most other forms of therapy, the data on which these treatments are used are very limited. Publication of additional, larger case series is therefore strongly encouraged, particularly if the observations are structured so as to provide information about possible dose–effects relationships, which may help determine the optimum dosage of a given drug for use in a subsequent randomized controlled trial.

In general, immunosuppressive therapy is often perceived to be in conflict with the clinical presentation of HS. This is however a view with a limited understanding of the disease process, which involves considerable, sterile inflammation. Therefore, as with many other dermatological conditions it may often be treated with anti-inflammatory or immunosuppressive therapies. In addition, these therapies offer the advantage of alleviating patient suffering effectively, if not permanently.

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Chapter 19

Zinc and Other Experimental Medical Treatments

19

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Key points

- New drugs are being studied for the medical therapy of hidradenitis suppurativa (HS)
- Zinc salt may have an anti-inflammatory effect in HS
- Botulinum toxin may play a role in the treatment of HS

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19.1 Introduction

Zinc salts have been used for a long time in the treatment of mild and moderate acne. The usual dose is between 30 mg and 60 mg zinc metal daily (corresponding to two – and four respectively – capsules of 15 mg zinc gluconate per day in France). Clinical studies have shown a significant effect of zinc salts mainly on inflammatory lesions (superficial and deep lesions). Zinc gluconate was about 15% less effective than minocycline in a randomized trial [12].

In Verneuil's disease, the drugs usually prescribed in acne (cyclines, isotretinoin) are poorly effective, and a need for additional therapy exists. So, owing to the in vitro anti-inflammatory effect of zinc and its clinical efficacy against inflammatory, even nodular, acne lesions, zinc gluconate has been used in Verneuil' s disease.

19.2 Zinc Salts

19.2.1 Mechanisms of Action: Modulation of the Proliferation and Differentiation of Keratinocytes and Cell Apoptosis

Zinc is a cofactor of many metallo-enzymes [1] implicated in the replication of DNA, gene transcription, RNA and proteomic synthesis. Thus, it increases the proliferation of keratinocytes and modulates their differentiation. This physiological role is altered by a severe shortage of zinc [2] (congenital or acquired). At the clinical level, it induces an ichtyosiform aspect of the skin, which is, moreover, atrophic. At the histological level, a parakeratosis aspect is noted, with necrosis of keratinocytes, and at the electron microscopy level a decrease of keratohyalin granules and tonofilaments in the keratinocytes is observed.

In the dermis, zinc also stimulates the proliferation of fibroblasts, increasing collagen and elastin production. This is mainly related to its action on lysyl oxidase. In addition, it is a coenzyme of several metallo-enzymes of the dermis.

Zinc also has a role in the apoptosis of keratinocytes. In vitro, the addition of a chelator of zinc to the culture medium decreases the nuclear concentration of zinc in keratinocytes, inducing cell apoptosis. This activity is related mainly to its role as a co-enzyme of different transcriptional factors implicated in apoptosis, such as P53 or FP1 (ferroportin 1). In addition, zinc, as an antagonist of calcium, inhibits the activation of "endonucleases", which have an anti-apoptotic activity. Recently it has been shown that zinc salts stimulate the production of insulin-like growth factor, which induces the proliferation of keratinocytes in the epidermis.

19.2.2 Anti-Inflammatory Activity

Zinc's efficacy in Verneuil's disease is probably due to its anti-inflammatory activity. It has activity against various targets implicated in the cutaneous inflammatory reaction and the mechanism of action is still only partially understood.

As for non-specific immunity, 30 mg zinc metal [3] inhibits the chemotactic migration of granulocytes, both in vitro and in vivo. It activates natural killer cells and the phagocytic function of granulocytes [4].

Zinc also inhibits the expression of integrins by keratinocytes in inflammatory lesions, i.e. ICAM 1 and LFA 3, which play an important role in the interactions between keratinocytes and lymphocytes [5].

The production of two main inflammatory cytokines produced by keratinocytes in inflammatory lesions, namely tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6), is inhibited by zinc salts [6]. In addition, zinc has an anti-oxidant activity, by inducing the expression of the enzyme Zn-Cu superoxide dismutase, which is present in keratinocytes and fibroblasts; thus, it increases the elimination of free radicals. As for T-cell-mediated immunity, zinc is a cofactor of thymulin, which is a thymic cytokine implicated in the maturation of T lymphocytes.

19.2.3 Activity Against 5α-Reductase

Zinc salts have anti-androgenic activity, by inhibiting the activity of 5α-reductase type I and II (mainly I in vitro [7]). This enzyme induces the transformation of testosterone to dihydrotestosterone, which binds to androgenic receptors expressed by sebaceous glands stimulating the production of sebum. This activity remains to be demonstrated in vivo.

19.2.4 Healing

Zinc stimulates the migration of keratinocytes, which play an important role in the healing of cutaneous wounds, by stimulating α3, α5 and β1 integrin functions [8, 9].

19.3 Zinc Salts in Verneuil's Disease

Until now there have been no reports on zinc's efficacy in HS. At the Department of Dermatology of Nantes (France), we have treated 22 patients with Verneuil's disease with zinc gluconate (Rubozinc®) [10].

In total, 15 women and 7 men were included in the study. The mean age was 38.3 years, the mean age at the onset of lesions was 24. 6 years and the mean duration between the beginning of the illness and diagnosis was 6.5 years. Eleven patients were at Hurley's grade I, 10 at grade II, and 1 at grade III. Zinc gluconate was used at a dose of six capsules of 15 mg zinc gluconate per day (Rubozinc®). The mean follow-up was 23.7 months. Results were assessed depending on the degree of remission.

Of the included patients 8/22 (36%) experienced complete remission. Complete remission was defined as no new lesions for 6 months or more (Figs. 19.1, 19.2). For these patients an attempt to decrease the doses of zinc was made but relapses were seen at a dose of between two and four capsules. Recurrences disappeared when the dosage of zinc salts was increased again. Thus, the treatment appears clearly to be suppressive rather than curative. A dose–response relationship may be present, as it would

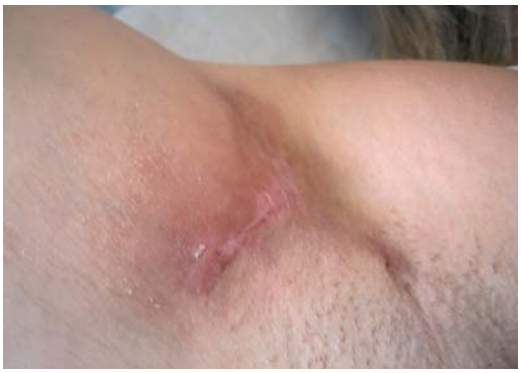

Fig. 19.1. Before treatment

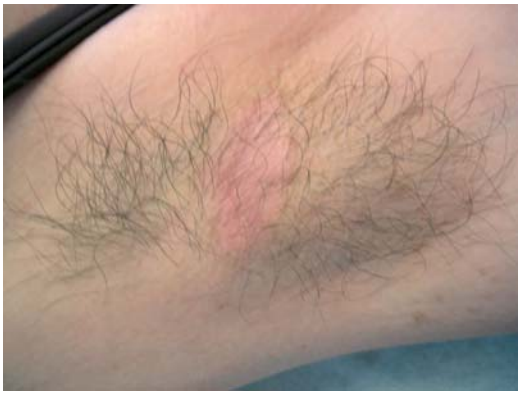

Fig. 19.2. After 6 months of zinc gluconate, six capsules/day

appear that a clinically suppressive effect only occurred at high doses.

Partial remissions were seen in 4/22 (18%) patients. Partial remission was defined as a decrease in the number of nodules and a shorter cycle of each inflammatory lesion, based solely on the patient's opinion. For an outcome to be classified as a partial remission, the patients' assessments should remain stable for 1 year.

Stabilization was defined as no progression under treatment, and categorized as the lesser of the positive outcomes. Almost half (10/22, 45%) of the included patients experienced stabilization. None of the patients experienced deterioration of their HS during treatment. Gastrointestinal side-effects (diarrhoea, gastralgia, nausea, abdominal pains) were noted in four patients. One patient had to stop the treatment.

The efficacy of zinc salts in Verneuil's disease probably relies mainly on its anti-inflammatory activity. A similar effect is seen in acne, where zinc salts are used at a lower dose (30 mg metal zinc) and treatment appears to be brought about essentially by action on inflammatory lesions [11, 12]. A prospective study is now ongoing to confirm this preliminary result.

19.4 Other Experimental Drugs

Apocrine glands produce sweat, which becomes smelly after bacterial degradation. Heckmann et al. [13] reported that botulinum toxin may decrease the production of sweat by apocrine glands, similarly to the effect on eccrine glands. The mechanism is related to the cholinergic stimulation of apocrine glands, which is inhibited by the botulinum toxin. Although based on an erroneous concept of apocrine gland involvement, botulinum toxin has been tried in the treatment of HS. Two cases of treatment of Verneuil's disease (HS) with botulinum toxin have been reported [14].

The first patient was a 29-year-old woman with recalcitrant HS, who experienced relapses after isotretinoin, zinc gluconate and antiandrogen therapy. The lesions were located in the axillary regions and mammary folds. Botulinum toxin A (Botox®) was injected at a dose of 50 units in each axillary region and 10 units in each of the mammary folds. A complete remission was observed after 1 month. The duration of the effect was 6 months, with a disappearance of the lesions after new injections.

The second patient was a 24-year-old woman who had experienced a minor therapeutic effect of antiandrogen and isotretinoin treatment. In her case botulinum toxin (100 units) was injected in the left axillary region, allowing a left–right comparison of the effect. A clinical effect was observed as soon as 15 days after the injection. The right side was subsequently injected with 100 units 1 month later, when the difference between the two sides was dramatic. The nodules recurred after 6 months, disappearing after a new injection of botulinum toxin. Later, the same treatment was successfully used in the pubic region of the patient.

Although based on an erroneous understanding of the tissues involved in HS, these serendipitous observations appear promising, and need confirmation in more structured trials. The possible mechanism may also be interpreted to be a reflection of reduced eccrine sweat gland activity, which leads to reduced sweating and thereby indirectly to a reduction of the shear forces on the surface of the skin and the hair follicles. The appropriate doses must also be identified more precisely. Finally, the potential side-effects after several injections should be studied, as the treatment appears only to be suppressive, with a 6 months duration of effect.

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Chapter 20

Biologics For Hidradenitis Suppurativa (Verneuil's Disease in the Era of Biologics)

20

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Key points

- Hidradenitis suppurativa (HS) is resistant to current medical management options
- The association with Crohn's disease (CD) suggests an inflammatory etiology
- Infliximab has been shown to induce durable remissions in patients with HS and HS/CD
- The efficacy of infliximab suggests a role for tumor necrosis factor alpha (TNFα) in the etiology and pathogenesis of HS
- The efficacy of infliximab in HS suggests a role for broadening the therapeutic applications of TNFα inhibitors

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20.1 Introduction

Verneuil's disease, better known as hidradenitis suppurativa (HS), is a chronic inflammatory disease that is clinically hallmarked by multiple abscesses and sinus tracts distributed in areas densely populated with apocrine glands. Stage I HS is characterized by the presence of abscesses without scarring or sinus tracts. With progression to Stage II, scarring and sinus tract formation are seen. By definition, patients with Stage III disease have multiple interconnected sinus tracts and scarring, typically involving multiple regions [1]. The significant morbidity of this disease is important, and is emphasized further by the limited effectiveness of the currently available "standard" medical therapies, including antibiotics (Chap. 15), antiandrogens (Chap. 16), retinoids (Chap. 17), immunosuppressants (Chap. 18), and/or complementary and alternative medicines (Chap. 19) [2].

20.2 Background

Similar to most chronic diseases in the current medical milieu, there is a constant interplay between therapeutics and pathophysiology. With the development of novel therapeutic agents with specific mechanisms of action and the knowledge of such mechanisms, new inroads have been made into our understanding of the pathophysiology of several diseases. This in turn has spawned further development of medical pharmacological therapies. The closer we get to understanding the molecular mechanisms of a disease, and in particular of HS, the greater our opportunity to pinpoint directed medical management. Nowhere does this ring more true

Table 20.1. Biologic therapy in HS [5, 8–11]. (*CD* Crohn's disease, *CR* case report, *CS* case series, *HS* hidradenitis suppurativa, *PC* personal communication, *UC* ulcerative colitis)

Author	Case report no.	Year	Strength of evidence	Age (years)/ sex	Disease duration (years)	Biologic	Outcome measures	Outcomes
Martinez et al. [8]	1	2001	CR	30/F, HS + CD	6	Infliximab	Resolution of refractory nodules	Remission 6 months after two infusions, maintained with azathioprine (adverse reaction noted after 2nd dose)
Katsanos et al. [5]	2	2002	CR	39/M HS + CD	Unknown	Infliximab	Remission	Remission after 2 years of infusions
Lebwohl and Sapadin [9]	3	2003	CR	21/M HS +/– CD	2	Infliximab	Complete re-epithelialization	Disease resolution
Adams et al. [10]	4	2003	CR	17/M HS + UC	3	Infliximab	Complete remission	Complete resolution of pain, tenderness, purulence, draining and odor Induction of disease remission
Adams et al. [10] (K.B.G.)	5	2003	PC	Unknown HS	Unknown	Infliximab	Remission	Successful remission
Sullivan et al. [11]	6–10	2003	CS	51/F 28/F 36/F 57/F 45/M All HS	20 10 20 44 25	Infliximab	Patient reported disease activity scale Ability to decrease "standard" systemic medications (ciclosporin, prednisone)	Patients' reported disease activity significantly decreased within 3–7 days (p=0.0001) paired t test Patients reported decreased pain after 24 h
Rosi et al. [12]	11	2005	CR	30/F HS + CD	1.5	Infliximab	Improvement of symptoms	No evidence of active inflammation 5 weeks into therapy

than for the new biologic therapies. This is particularly important in HS, given that there is no universally effective medical therapy, and, furthermore, current medical management is marginally beneficial even when claimed to work.

20.2.1 Crohn's Disease and Hidradenitis Suppurativa Co-Occurrence: A Rationale for Anti-TNF Therapy

While the etiology and pathogenesis of HS remain largely unknown, the disease has been shown to occur in association with other disorders of follicular occlusion, such as acne conglobata and dissecting cellulitis of the scalp. In these disorders, follicular occlusion leads to overgrowth of bacteria and subsequent neutrophilic inflammation. Many observations have been reported regarding the role of androgens/hormones, obesity, and genetics, which may in addition influence the clinical picture [3, 4]. It is the reported association with Crohn's disease (CD), however, which has led to speculation and opportunities for novel management. It has been postulated that the two conditions share similar pathological immune mechanisms, such as increased levels of tumor necrosis factor alpha (TNFα) and neutrophilic chemotaxis [5]. This interesting co-occurrence of HS and CD highlights both the inflammatory nature of the disease and the rationale for using biologics known to be effective in CD [6].

There is evidence that infliximab is efficacious at stopping fistula drainage when used as a maintenance agent in fistulizing CD [7]. It is reasonable to suppose that if a patient sees infliximab-induced improvement of their CD fistulization, they would also see the healing of any co-existing HS with skin fistulization. A review of the literature demonstrates that this is indeed the case. The first three cases of effective treatment of HS with infliximab were in patients who had undergone the treatment for CD. At the time of writing this chapter, 11 cases of HS treated with infliximab have been reported in the literature. Of the 11 reported cases, 4 (36%) had been patients with associated CD (see Table 20.1) [5, 8–12]. Nevertheless, these preliminary cases demonstrate both the high degree of efficacy of infliximab therapy for longstanding HS and that in some cases improvement was observed in as little as 3 days.

20.3 Anti-TNF Drugs in HS

Infliximab is the only biologic with reported use in HS. It is a chimeric monoclonal antibody with high affinity for TNFα. The molecular structure encompasses the human IgG constant region spliced with a murine variable antigen-binding region. This therapeutic antibody scavenges free TNFα, neutralizing its proinflammatory biological effects. Mitigation of the target immunological endpoints for TNFα include:

1. Induction of proinflammatory cytokines interleukin-1 (IL-1), IL-6, and IL-8
2. Activation of neutrophils, lymphocytes, and eosinophils
3. Upregulation of adhesion molecule expression by endothelial cells [13, 14]. Additionally, infliximab binds membrane-bound and receptor-bound TNFα leading to complement-induced antibody-mediated CD4+ T cell cytotoxicity.

Infliximab is currently approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid and psoriatic arthritis, Crohn's disease and ankylosing spondylitis. Many off-label uses of this agent have additionally been reported in the literature and not surprisingly many relate to inflammatory skin disease.

The drawbacks to infliximab therapy are few. Commonly reported side-effects include diarrhea, headache, pharyngitis, upper respiratory tract infection, and urinary tract infection [15–20]. Rare instances of re-activation of tuberculosis (TB), aseptic meningitis, systemic lupus erythematosus and antibody-mediated anaphylactic shock have also been reported. In the 147,000 cases throughout the world that have received infliximab that Keane et al. [21] reviewed in 2001, there were 70 cases of TB, and approximately 60% of these represented extrapulmonary disease. The current understanding suggests that re-activation of TB is associated

with disruption of the immune system's ability to compartmentalize the bacilli in granulomas and inhibition of macrophage apoptosis. Thus the FDA requires that patients have a negative purified protein derivative (PPD) test prior to the onset of infliximab therapy. Infusion-associated anaphylactoid reactions, while rare, can be avoided by slowing the infusion rate and pretreating the patients with antihistamines and steroids.

Antibody formation can be seen with long-term use and is inversely proportional to total infliximab dose. The concern regarding the development of antibodies to infliximab with long-term use follows the observation that 13% of Crohn's patients treated with repeated infusions had indeed formed antibodies [22]. As expected, loss of clinical efficacy accompanies the antibody formation, as does the development of infusion-related chest pain, bronchospasm, and anaphylactic shock. The development of antibodies can be reduced by treating the patients on a scheduled, regular basis (i.e., every 8 weeks) and with the concomitant use of low-dose immunosuppressants [16].

In the reported cases of HS treated with infliximab therapy, the demographics for ten patients are known (one case was reported without specifications) (see Table 20.1) [5, 8–11]. Four patients were reported to have had concurrent CD. Patients' age ranged from 17 to 57 years with a mean age of 35.4 years. There were four men and six women. HS disease duration was reported as being between 1.5 and 44 years, with a mean duration of 14 years. As the majority of the reports are single case reports of successful therapy, long-term effects were not known or described. Importantly, 9 of the 11 patients reported a significant reduction in disease activity within 5 weeks of infliximab infusion therapy. The five patients treated in a dermatological inpatient ward were observed to have marked or moderate improvement within 3–7 days after each infusion [11].

20.4 Future Prospects

While no specific reports exist regarding the other FDA-approved anti-TNF agents on the market, one of the authors (F.A.K.) has treated two patients with HS with etanercept. The patients appeared to improve, however not as markedly as seen with infliximab. This is not surprising given that etanercept has not been found to be effective in CD. The other anti-TNF agent approved by the FDA, namely adalimumab, has not been reported in association with

Table 20.2. Biologics used in CD [22–24]. (*AS* Ankylosing spondylitis, *CD* Crohn's disease, *JRA* juvenile rheumatoid arthritis, *PsA* psoriatic arthritis, *Pso* psoriasis, *PsoA* psoriatic arthritis, *RA* rheumatic arthritis, *TNF* tumor necrosis factor, *UC* ulcerative colitis)

Generic name	Company	Subset	Structure	Target	FDA indication
Infliximab	Centocor	IgG1	Chimeric: human Fc and murine Fab	TNFα, complement fixation, T cell apoptosis	CD, RA, AS, PsA
Adalimumab	Abbott	IgG1	Fully human	TNFα, complement fixation, T cell apoptosis	RA CD Phase III
CDP571	Abbott	IgG4	Humanized, murine complementarity determining region	TNFα, decrease C reactive protein, no complement fix	CD failed Phase III UC Phase IIa
CDP 870	UCB	–	Humanized Fab, linked to polyethylene glycol	TNFα, no complement fix	CD Phase III
Etanercept	Amgen/ Wyeth	Receptor IgG1	Human Fc backbone	TNFα, TNFα	RA, AS, JRA, Pso, PsoA CD failed Phase II

treatment of HS; additionally, CDP571 is in phase III trials for CD (see Table 20.2) [22–24].

If we are to follow the infliximab lead, it stands to reason that agents shown to be promising in CD clinical trials, such as the fully human IgG1 anti-TNF monoclonal antibody adalimumab and the fully humanized anti-alpha4 integrin IgG4 antibody natalizumab, would offer opportunities for effective management of HS [7] (see Table 20.2) [22–24]. At this time, the efficacy of these agents in inflammatory disorders such as rheumatoid arthritis has proven impressive and the short-term side-effects have been minimal with regard to the risk/benefit ratio. As we proceed to develop our experience and monitor the long-term effects, we are presented with determining the utility of each biologic therapy and ultimately finding the most appropriate disease–therapeutic pairing. Not all biologics are equally effective, but finding the optimal target disease may level the playing field.

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Chapter 21

Topical Treatment

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21

Key points

- Effective local treatments exist
- Local treatment may be sufficient for some patients
- Different local treatments can be combined for better effect
- Local treatment should be part of a systematic treatment plan for each patient
- If local treatment does not control the disease adequately within 3 months a more aggressive treatment, in combination with continued topical therapy, should be used

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21.1 Introduction

Topical or local therapy is traditionally often used in dermatology. It holds a number of advantages over systemic therapy, primarily by reducing the risk of a number of side-effects and being easy for the patients to administer themselves, but also its low cost. On the other hand, topical or local therapy is often less potent than systemic therapy when dealing with more generalized or recalcitrant diseases. Accurate assessment of disease severity is therefore of importance when choosing therapy.

In hidradenitis suppurativa (HS), topical therapy is best used in very early lesions or for the maintenance of a therapeutic result. In contrast, intralesional or local therapy is better suited for early advancing or intermediate lesions, before switching to surgery or systemic therapy. The choice of topical/local versus systemic therapy therefore depends not only on the individual characteristics of the patient and the disease, but also on the developmental stage of the disease.

Several different types of topical therapy have been tried in HS, although there are few actual trials. The paucity of trials opens the possibility of biased reporting of results, and therefore slows the development of new treatments. Antibiotics have been extensively used, and form a mainstay of early therapy with some of the few controlled trials in HS. Keratolytics have also

been used because of the histological similarities between HS and acne, although the evidence base for this is more restricted. Finally, anti-inflammatory preparations are on occasion helpful to patients when applied to predisposed areas as preventive or adjuvant therapy. In contrast, intralesional therapy with corticosteroids is frequently used, and often effective at treating individual recalcitrant lesions.

Failing local pharmacological therapy, minor local surgical procedures may be of help to some patients. This spectrum of therapies will be reviewed in this chapter.

21.2 Antibiotics

The significance of bacterial findings in HS is controversial. While bacteria are likely to be involved in the pathogenesis to some extent, it is probably in a role similar to that in acne in early lesions. In later stages of the disease bacterial infection seems to be a risk factor for the destructive scarring and progression of HS lesions. Coagulase-negative staphylococci are the most common bacteria found in cultures from the deep portions of HS lesions, as seen following carbon dioxide laser surgery [1]. An extensive review of HS bacteriology is found in Chaps. 11 and 15. Although the influence of bacteria is unclear, topical as well as systemic antibiotics are frequently used in treatment of HS.

There are two published randomized controlled trials of topical treatment of HS, both of them evaluating the use of clindamycin [2, 3]. Clemmensen [2] included 30 patients with HS of axillae and/or groin. In total 27 patients (21 women, 6 men) of mean age 31.3 years and mean duration of HS 5.5 years were included in the study. The patients were stratified according to the severity of HS, but the overall disease activity was moderate. A double-blind trial was performed with either a solution of clindamycin hydrochloride 1% in a vehicle of isopropanol 80%, propylene glycol 10% and water 9%, or placebo (vehicle) applied for 12 weeks. The patients were evaluated every 4 weeks and the number of pustules, inflammatory nodules, and abscesses were counted. Self-assessment by the patients was made in diaries by recording the intensity and number of elements, as well as the frequency and duration of recurrences. An overall estimation of the effect of treatment was based on a cumulated score of the parameters recorded (patient's assessments, number of inflammatory nodules, abscesses, and pustules). In all, 13 patients received active treatment and 14 received placebo. An overall improvement was seen in the clindamycin group at each monthly evaluation, and statistically significant improvement was found in the clindamycin group for each parameter except for inflammatory nodules at 1 and 2 months of treatment. Clindamycin was more effective than placebo.

Jemec and Wendelboe [3] compared topical clindamycin with systemic tetracycline in a double-blind, double-dummy controlled trial. In total 46 patients with HS stage I and II disease, according to Hurley's classification, were included, of which 34 (28 women, 6 men) were available for evaluation. After computerized blinded randomization the patients received a minimum of 3 months of therapy with active systemic plus topical placebo or systemic placebo plus active topical treatment. The active systemic treatment consisted of tetracycline 1 g (capsules 250 mg, 2×2) daily per os; active topical, 1% clindamycin phosphate in a vehicle of propylene glycol, isopropyl alcohol and water, applied twice daily. Uniform containers, placebo tablets and placebo lotion were used. At monthly visits the following outcome variables were evaluated: patient's global evaluation using a 100-mm visual analog scale (VAS) score, VAS score of soreness, physician's global evaluation (VAS score) and the number of abscesses and nodules. No significant differences were found between the two treatments, but significant changes occurred in the course of the study. Abscesses were reduced during the first 3 months of the study while nodules became reduced in numbers after 3 months of treatment. There was a progressive improvement in both the patient's and the physician's overall assessment, although the VAS score of soreness did not change during the study.

21.2.1 Topical Clindamycin

Clindamycin is a lincosamide antibiotic that is bacteriostatic and works by inhibiting protein synthesis in sensitive bacteria. Its antibacterial spectrum includes Gram-positive bacteria, in particular the genera *Staphylococcus* and *Streptococcus*, and several of the anaerobic bacteria. Clindamycin also suppresses the complement-derived chemotaxis of polymorphonuclear leukocytes (in vitro), thereby reducing the inflammation potential [4]. Topical clindamycin 1%, which is widely used in the treatment of acne, is applied to affected areas once or twice daily. Absorption of topically administered 1% clindamycin is estimated to be 1–5% [5]. Adverse effects are mostly local: irritation, erythema, peeling, itching, dryness, and burning. As rare events, episodes of diarrhea and even two cases of pseudomembranous colitis have been reported after topical clindamycin treatment [6, 7].

One complication of the use of topical antibiotics is the development of bacterial resistance. The number of patients carrying *Propionibacterium acnes* and *Staphylococcus epidermidis* resistant to topical antibiotics has increased over the last few years. A potential risk is the transfer of resistance to other bacteria, specifically *Streptococcus* spp. and *Staphylococcus aureus* [4]. In acne therapy it is now often recommended to use topical antibiotics for shorter periods and preferably in combination with topical retinoids, benzoyl peroxide or azelaic acid to enhance the efficacy and slow down the development of resistance [8].

The two randomized controlled trials referred to above [2, 3] have shown the effect of topical clindamycin used in mild or moderate cases of HS. The results of these studies fit well with the experience of more than 300 cases of HS treated at the Department of Dermatology, Karolinska Huddinge, Stockholm, Sweden. Clindamycin, preferably combined with azelaic acid, effectively suppresses acute exacerbations of at least milder forms of HS. The therapeutic effect of clindamycin on HS could be due to bacteriostatic as well as anti-inflammatory effects. There are other commercially available topical antibiotics including erythromycin, mupirocin and neomycin, which probably have been tested for HS treatment although, to our knowledge, there are no published reports and their clinical effects on HS remain to be shown.

21.3 Keratolytics

HS is a disease of the hair follicle with histological signs of poral occlusion [9–11]. Although there are only a few publications about the use of keratolytics in HS [12, 13], the follicular occlusion brought about by hyperkeratosis may be a therapeutic target. Therefore, by analogy to acne, this also appears to be a good target for keratolytics. In acne, another disease of the follicle with abnormal keratinization (microcomedo), the mainstay in classical therapy of early lesions is topical treatment with peeling agents, especially topical retinoids [8, 14, 15]. Here, the rationale is that all acne lesions arise out of a comedo and so it makes sense to treat acne patients with comedolytic agents [8, 14, 15]. Topical comedolytic agents are also recommended for use in maintenance therapy in acne by some authors [8, 14, 15].

Although topical retinoids such as tretinoin, isotretinoin, adapalene and tazarotene are strongly recommended in the management of most patients with acne vulgaris, there are currently no reports about the use of these comedolytic agents in HS. One possible reason for this is that the relatively weak peeling effect (considered as a side-effect) of topical retinoids is not strong enough for therapy of HS lesions. Another reason could be that physicians do not believe that a topical peeling agent can have any therapeutic influence on deep-seated nodules and sinus tracts of HS.

21.3.1 Resorcinol as a Keratolytic Agent in Hidradenitis Suppurativa

In the Netherlands, we have been gathering experience with the use of topical resorcinol for the treatment of HS since the 1970s [16]. Since 2000, two case series have been published about this topic, see Table 21.1 [12, 13].

Resorcinol [(BP, USP) $C_6H_4(OH)_2$,1,3-dihydroxybenzene] is a phenol derivative, used in

Table 21.1. Long-term response of HS to topical resorcinol. Outcome variables for pain and disease activity as felt by the patients as well as judged by the physician. Outcome in "longest follow-up" only concerns the score for resorcinol treatment (as given mainly by the patient) and not for surgical intervention and/or medication. [*AB* Antibiotics, *Re* retinoid (isotretinoin)]

Patient no., age (years), sex	Duration of HS (years)	Area of HS, Hurley stage	Improvement score[a]	
	–	–	At the end of treatment (2 months)	Longest follow-up
1, 17, F	3	Groin, 2	+ 2	AB, Re, + 1, 6 years
2, 30, F	9	Mixed, 2	+ 3	Deroofing, + 3 , 1 years
3, 32, F	3	Mixed, 2	+ 2	Deroofing, + 1 , 2 years
4, 39, F	2	Mixed, 2	+ 2	+ 2, 1 years
5, 40, F	1	Mixed, 2	+ 2	Deroofing, + 2 , 1/2 years
6, 39, F	4	Groin, 2	+ 2	+ 3, 1 years
7, 36, F	8	Mixed, 2	+ 2	Surgical excision, 0, 2 years; resorcinol stop
8, 25, F	1	Mixed, 2	+ 2	+ 2, 1/2 years
9, 50, M	6	Mixed, 2	+ 2	AB, Re, + 1, 1.5 years, resorcinol stop
10, 31, F	7	Mixed, 2	+ 2	AB, Re, deroofing, + 2, 5 years
11, 20, F	4	Mixed, 2	+ 2	Deroofing, + 2, 3 years
12, 30, F	6	Mixed, 2	+ 1	AB, Re, 0, 3 years, resorcinol stop
13, 37, F	8	Mixed, 2	+ 2	Deroofing, + 2, 2 years
14, 25, F	1	Mixed, 2	+ 1	Deroofing, + 1, 3 years
15, 28, F	7	Mixed, 2	+ 2	Surgical excision, + 1, 4 years
16, 33, F	2	Mixed, 2	+ 2	Deroofing, + 2, 3 years
17, 24, F	2	Axillae,2	+ 2	Deroofing, + 3, 2 years
18, 30, F	8	Mixed, 3	+ 1	Surgical excision, + 1, 1/2 years, resorcinol stop
19, 46, F	24	Mixed, 3	+ 1	Surgical excision, + 1, 1/2 years, resocrinol stop
20, 30, F	12	Mixed, 3	+ 1	Surgical excision, + 1, 4 years
21, 28, F	10	Mixed, 3	+ 1	AB, Re, surgical excision, + 1, 1/2 years, resorcinol stop
22, 40, F	19	Mixed, 3	+ 2	AB, surgical excision, 0, 3 y, resorcinol stop
23, 38, F	15	Mixed, 3	0	Resorcinol stop
24, 34, F	16	Mixed, 3	+ 2	Surgical excision, + 1, 1 years

[a] Improvement scores: *+3* clear, *+2* marked improvement, *+1* improvement, *0* no change.

dermatology for more than 100 years because of its antipruritic, keratolytic and antimycotic properties [17] (see Fig. 21.1). Topical drugs including resorcinol are nowadays mainly used for the treatment of acne vulgaris as a peeling agent [17–19], at concentrations of 5–15% in creams, fat or drying pastes [17].

The data on resorcinol in acne are variable. In a screening program searching for effective drugs in the treatment of acne, it was concluded that resorcinol lotion was an ineffective agent [20, 21]. The studies, however, used only low concentrations of 5% and 10% resorcinol [20, 21], which may be too low and therefore intro-

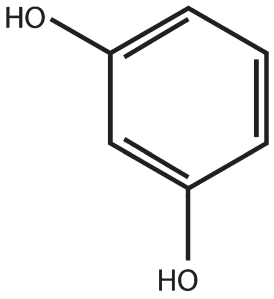

Fig. 21.1. Resorcinol [$C_6H_4(OH)_2$]. Synonyms: *m*-dihydroxybenzene; 1,3-benzenediol; resorcin; 1,3-dihydroxybenzene; 3-hydroxyphenol; *m*-hydroxyquinone; *m*-benzenediol; 3-hydroxyphenol

duce false-negative results. It is known – mainly from the German literature – that the peeling effect of resorcinol starts only at a concentration of 10% or more [22]. Also, from our own experience, we have observed that 10% resorcinol in an oil-in-water (o/w) cream used for patients with HS causes no, or at the most minimal, desquamation. In the overwhelming majority of patients the peeling effect starts only at a concentration of 15% and will almost always be present at a concentration of 20%–25% [12, 13]. In prescription regulations for treatment of acne, a resorcinol concentration of 20% is recommended in peeling pastes [22, 23].

In high concentrations, resorcinol has a marked peeling effect. Siemens used resorcinol in concentrations of up to 30% to obtain peeling in acne conglobata [17]. Higher concentrations (35%–50%) cause a very strong keratolytic effect but are generally not used because of the associated danger of systemic toxicity.

21.3.1.1 Indications

It was found that HS patients referred to the secondary sector develop a median of two boils per month and that the individual duration of painful boils is about 1 week [24]. In the acute phase, many patients have very bad experiences lancing their painful boils, with later irrevocable recurrence. So there is a need for a fast-acting non-invasive boil treatment, preferentially performed by the patient himself or herself.

It has been observed [12, 24] that acute early single lesions of HS develop in three different ways: firstly, they can be permanently painful and fail to settle completely; secondly, the boils rupture and pain is relieved; and thirdly, the lesions resolve and pain disappears. After such an acute period the lesions remain inactive for a variable period, called the maintenance phase. Maintenance therapy therefore could be important in HS because the disease tends to recur without an ongoing treatment regimen. In addition, it may be hypothesized that the whole region – for example axillae and groin – can be thought of as an HS-prone area, which needs preventive therapy. It has been suggested that resorcinol targets lesions in the acute and maintenance phases as well the HS-prone areas generally [12, 13].

The above-mentioned could be substantiated by results in acne research, in which it has been shown that even normal-looking skin from acne patients may already be developing very early microcomedones. To treat acne, comedolytic therapies need to be applied topically to acne lesions, but just as importantly to the normal-looking skin of acne-prone areas [8, 15, 25]. It has been stated that maintenance therapy of acne sustains acne remission [8, 15, 25].

21.3.1.2 Mechanism of Action

Topical resorcinol targets the follicular keratin plug, a potential first event of all HS lesions. The concentration-dependent desquamation effect of resorcinol is strong; in practice it is obvious that resorcinol is a much more powerful agent than the current comedolytic agents, e.g., topical retinoids or azelaic acid (see Fig. 21.2).

It has been observed that in the acute (painful) phase of HS, the peeling agent resorcinol will cause an earlier breakthrough or an earlier resorption (shrinkage) of the lesions. In the maintenance phase, when the lesions are settled down, it may be hypothesized that drainage from the follicle is improved by the removal of hyperkeratosis. The discharge from the boils and sinus tracts will also be improved and lesions will leak minimal amounts of pus continuously. It may be speculated that this effect of

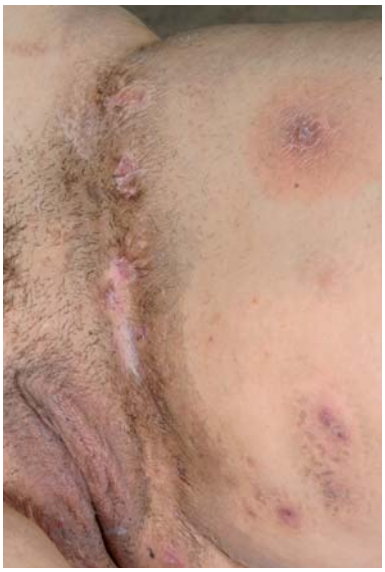

Fig. 21.2. Patient with HS after 6 weeks of treatment with resorcinol in increasing concentrations from 10% to 20% (in the maintenance phase decreased to 15%). The brown coloration (reversible) is a side-effect of resorcinol

resorcinol will ultimately result in a delay or lack of recurrences.

21.3.1.3 Side-Effects of Resorcinol

Resorcinol can cause cutaneous irritation, including erythema and sometimes substantial desquamation, depending on the resorcinol concentration and sensitivity of the patient's skin. The concomitant use of a simple moisturizer can minimize the irritation. Contact sensitization appears to be rare [26]. Resorcinol may produce (reversible) discoloration of the skin.

Systemic toxicity due to resorcinol through percutaneous absorption is extremely rare, but the physician must be aware of this potential risk [26]. Systemic toxicity has been reported in the older literature and in one recent case report in which high concentrations (40%–50%) were used in large measures for large (injured) surfaces [22, 27]. Two young adults were treated for acne vulgaris involving their entire back with, respectively, a daily quantity of 50 g ointment (= 20 g resorcinol) for 33 days and with 160 g ointment (= 80 g resorcinol) for 3 days. Following this, the patients presented recognizable toxic effects such as cold sweating, dizziness, collapse, purple-black urine, and hyperthyroidism [23]. There are also reports of acute poisoning in babies after percutaneous absorption of resorcinol, in two cases with a fatal outcome [28].

In conclusion, it can be stated that the use of resorcinol in concentrations up to 15% [17–19, 23] to 20% [17, 23] can be considered safe. In the past, these resorcinol preparations for patients with mainly acne, but also other skin diseases, were continued for months or years with little concern. As far as can be gathered from the (mostly older) literature, resorcinol concentrations of up to 30% can be used in a safe way for acne. Whether this is also valid for HS is unclear, because the HS lesions are situated mainly in the axillae and groin, which causes an occlusion effect. Therefore, we advise not exceeding a concentration of 20% resorcinol in general for HS therapy. Concentrations of 30% and more are too high for HS therapy because of the danger of systemic toxicity.

There are insufficient data on the use of resorcinol in pregnancy to assess the risk accurately. In answer to enquiries made to the Office of Side-effects of Drugs in the Netherlands it was stated that the Office did not know of any report in which a relationship between a birth defect and the topical application of resorcinol could be established, although this does not rule out the existence of such an effect.

There are at least two classification systems for drug safety in pregnancy, i.e., the Swedish (FASS) and the US (FDA) systems. Many older drugs, including resorcinol, have not been given a letter rating by their manufacturers, and the risk factor assignments were made by one of the authors (J.B.). In the Swedish (FASS) system resorcinol is placed in category B2, which includes drugs with limited experience in pregnant women, no increase in frequency of fetal malformations or other harmful effects; animal studies are inadequate or lacking. In the US (FDA) system, it is included in category C, which includes drugs whose risk cannot be ruled out because of inadequate data.

21.3.1.4 Treatment Schedule with Resorcinol Creams

One of the authors (J.B.) has frequently used the treatment schedule shown in Table 21.2 for patients with HS, mostly in patients with Hurley Stage II disease. Normally, resorcinol is used at a varying concentration of 5%–20% incorporated in an o/w cream with emulsifying waxes, i.e., cremor lanette II F.N.A. (Genfarma, Maarssen, The Netherlands). Resorcinol is incompatible with cetomacrogol creams [17].

Therapy with topical resorcinol is started at the patient's first visit at a concentration of 10%. The concentration of resorcinol is then increased at 1-week intervals, thus in the first week resorcinol 10% cream is applied twice a day. If there is no desquamation, the resorcinol concentration is increased to 15% in the second week and this treatment is then continued for a period of weeks.

With resorcinol 15% some degree of desquamation will normally be present, but if necessary the concentration can be increased to 20% to achieve an acceptable degree of desquamation. Once a peeling effect is achieved, the reduction or disappearance of pain will start in a few days instead of the average duration of 1 week, and the patients experience corresponding relief.

In cases where the lesions are completely or partially settled after 4–6 weeks of treatment, topical resorcinol is also the preferred agent for maintenance therapy. Here the patient is advised to apply the cream once a day every 2 or 3 days (twice a week) prophylactically. In the event of new activity the patient should immediately resume the resorcinol fast-acting boil-therapy strategy and increase the application frequency of resorcinol up to twice daily. Maintenance therapy is also strongly advised after successful initial therapy with, for example, antibiotics, surgical excisions in extreme cases or the deroofing method for sinus tracts and persistent boils [13, 29]. Patients should be informed very clearly about the multifocal character of the disease, i.e., in addition to the high risk of recurrence, there is also the possibility of developing new lesions in the same region at some distance from the original ones and also in other anatomical regions. Patients also need to understand that treatment with topical resorcinol in general does not cure the HS lesions, but clearly gives more control over disease activity.

Table 21.2. Treatment regimen for the use of resorcinol

1. Treat new inflamed lesions with resorcinol in increasing concentrations until peeling occurs
2. Once peeling occurs continue maintenance therapy of the lesions at unchanged concentrations (normally 15%)
3. Resorcinol at peeling strength (individually variable) can be used for twice-weekly prophylactic treatment of predisposed regions
4. The keratolytic treatment regimen can be used in combination with the deroofing method for sinus tracts and persistent boils, a conservative surgical technique with long-term oral antibiotic therapy and, in extensive cases, with surgical excision

21.3.1.5 Clinical Experience

There is more than 15 years of experience with this peeling therapy. In a multicenter pilot study more than 100 patients applied resorcinol once or twice daily to HS-involved areas for up to many years with the above-mentioned protocol (Table 21.2). In another study topical resorcinol cream in a vehicle was compared with the vehicle alone, by using the bilateral comparison technique (to be published). It was found that resorcinol was more effective than placebo.

The most striking effect noticed by the patient is the disappearance of the pain after approximately 2 days instead of the median time of 7 days. In addition the patients appreciate that they can apply resorcinol as a fast-acting boil therapy at the very first sign of a painful boil. The empowerment of patients to self-treatment may be an important factor in helping them to cope with this disease.

The result can vary from complete resolution of all symptoms (in exceptional cases) to a decrease in subjective complaints, mainly in the early stages of the disease (Hurley stages I and II), but it also depends on whether the patient has the discipline to continuing applying resorcinol cream as maintenance treatment. Some

patients with Hurley Stage III disease were initially enthusiastic about their pain relief, however in almost all cases this feeling fell away after a couple of months, mainly because of the ongoing widespread disease activity. Nevertheless, some patients continue the resorcinol treatment. Compliance is crucial for a good effect. The degree of symptom relief (pain, pus discharge, malodor) often makes it worthwhile for the patient to continue using the cream once the effect sets in. There is obviously no cure of sinus tracts and nodules may also persist. Overall, it is estimated that in approximately 80% of the patients (Hurley Stages I and II) the (subjective) complaints are relieved by this treatment. Moreover, the usefulness of this therapy has been supported by the continued patient demand for it. Formal contemporary studies are however necessary to substantiate these clinical impressions further.

21.4 Topical Anti-Inflammatory Therapy

No formal studies have been published on the use of topical anti-inflammatory treatment of HS. Experience nevertheless suggests that some preparations may prove useful to selected patients. The preparations tried are azelaic and fusidic acid, the latter both alone and in combination with topical corticosteroids (personal observation, G.B.E. Jemec).

21.4.1 Azelaic Acid

Azelaic acid occurs naturally on the skin. It is a straight-chained nine-carbon-atom dicarboxylic acid, which is non-toxic, non-teratogenic, and non-mutagenic [30]. It has numerous biological effects. These include inhibition of mitochondrial oxidoreductases of the respiratory chain and of enzymes concerned with DNA synthesis. Reportedly it has antiproliferative and cytotoxic effects on a variety of tumor cell lines in culture [31, 32]. In vitro it can influence the growth of keratinocytes and has antifungal and bacteriostatic effects [33, 34]. Clinically azelaic acid is registered for the treatment of mild acne and is used in hyperpigmentary disorders [35, 36].

In HS there are no formal studies of the effects of azelaic acid, but occasionally patients achieve control of their disease by using it as a preventive therapy. Typically the drug is used in combination with other treatments of acute lesions, e.g., topical clindamycin or intralesional steroids.

Azelaic acid is a very safe drug and its side-effects are correspondingly restricted to mild local irritation of the skin. The exact role of this drug in the treatment awaits formal studies.

21.4.2 Fusidic Acid

Fusidic acid is a steroid-like molecule with a strong anti-staphylococcal effect [37]. It is effective in the treatment of superficial infection, and may aid the treatment of superinfection in HS. However, on its own it is less effective in the treatment of primary HS lesions, presumably due to penetration problems. On occasion it may be useful for reducing inflammation and superinfection of established HS lesions, particularly when used in combination with a topical corticosteroid.

21.5 Intralesional Therapy

In contrast to topical therapy the use of intralesional anti-inflammatory therapy has been used more extensively. This therapy represents an intermediate form of treatment between pharmacological therapy and surgery. The intralesional injection of corticosteroids is aimed at reducing inflammation rapidly, and may even be suggested to have an atrophogenic effect on formed sinus tracts, which is desirable from a theoretical point of view. There is a long tradition of using this modality in acne cysts, where the results are often most convincing. Early studies found that low-dose therapy using intralesional triamcinolone for acne cysts was often as successful as more potent preparations, and carried less risk of atrophy or other complications [38, 39].

No proper studies of the effects of intralesional corticosteroids in HS are available. How-

ever, the use of local anti-inflammatory treatment is in good accordance with the use of systemic anti-inflammatory therapies (see Chap. 18), and the low prevalence of recognized pathogenic bacteria.

In practice this is particularly useful for patients with few intermediate lesions, and may often be combined with topical therapy to keep the disease under control.

If there is clinical suspicion of suprainfection with, for example, *Staphylococcus aureus* this treatment is not recommended. Patients with *S. aureus* infection are often characterized by rapidly evolving, painful, red, and suppurating lesions.

When using this treatment 0.5–1.0 ml triamcinolone (10 mg/ml) is injected into the lesions with a no. 27 or thinner needle. Weaker concentrations of triamcinolone may also be useful, whereas betamethasone has been reported as being less effective in acne lesions [38]. On occasion the injected triamcinolone will leak from the sinus tract, and paralesional injections may therefore also be used. The use of intralesional steroids has been successfully combined with topical and systemic use in the treatment of acne sinus tracts, and may also be combined with systemic therapy in the treatment of HS [39].

Relief usually occurs within days of the injection. In early lesions it is the author's (G.B.E.J.) impression that resolution of nodules may occur, whereas more developed boils respond with spontaneous drainage after a few days, offering relief similar to that reported with the use of strong keratolytics.

21.6 The Use of Local Therapy

Initial treatment of early or minor lesions is usually local. Provided the local therapy is part of a therapeutic strategy for each patient, this is a rational approach, in terms of both traditional clinical assessments such as effect and cost-efficiency and also cost-benefit to the patient. Efficient forms of local treatment exist, although none is universally effective. They have a low potential for side-effects and many can be used for both prophylactic therapy and self-treatment of early lesions. Self-treatment of early lesions is further indicated because this group of patients is very well acquainted with the natural evolution of lesions, and can therefore start therapy at a very early point in any flare of the disease.

Local treatment can be carried out as monotherapy, but most often a better result is achieved by combining several treatment modalities, such as topical antibiotics and intralesional steroids. By combining local therapies with different mechanisms of action it may be possible to contain disease progression without having to use systemic therapies or surgery. Just as for other therapies the long cycles of HS require that a therapy is used for at least 3 months before its efficacy can be adequately assessed. It is therefore of benefit to the patient and the treating physician if a plan for the containment of the disease is drawn up for each patient. If the disease is progressive treatment should be intensified every third month until adequate relief is achieved. This could involve progressively more aggressive therapy, starting with topical therapy and moving on in a predetermined manner to combinations of topical therapies, to intralesional steroids, to systemic therapy and then to surgery.

21.7 Publication Bias

The paucity of controlled trials is apparent for local therapy of HS. There is therefore a strong bias towards anecdotal therapies. For anecdotal therapies there is a strong and well known bias towards false-positive reports.

In this review of treatments the authors have attempted to assess the local therapies in view of personal experience with the treatment modalities, but this does obviously not substitute for controlled trials or careful follow-up studies of cohorts of patients.

Just as in the development of new surgical techniques a lower degree of evidence is acceptable in order to establish the necessary data for planning a future trial and providing immediate information. The key features of any investigations should therefore be an explicit randomization procedure, appropriate documentation and a follow-up of not less than 3 months.

For bilateral HS lesions randomized intra-individual left to right comparison of physical therapies is possible, but it is not advised to directly compare axillary and genitofemoral lesions, for example, as their natural prognoses often differ significantly (it is better for axillary lesions).

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Chapter 22

Surgery

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22

Key points

- The surgical method chosen in each case depends on several factors, including the region(s) involved, as well as the type and severity of hidradenitis suppurativa (HS)
- Incision and drainage may sometimes lead to temporary control of symptoms but is best avoided since the abscesses almost inevitably recur
- Simple excisions with primary closure or exteriorization, curettage and electrocoagulation of the sinus tracts may be sufficient in milder forms
- Wide and radical excision, well beyond the clinical borders of activity, serves as the golden standard treatment, regardless of the localization of HS
- Vaporization with carbon dioxide laser is a sufficient surgical method for early treatment in moderate forms
- Healing by secondary intention is a convenient alternative to reconstruction using skin grafts or flaps

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22.1 Introduction

Hidradenitis suppurativa (HS, synonym acne inversa) is a cicatrizing and frequently persistent inflammatory disorder of the sebaceous follicles and terminal hair follicles of apocrine-gland-bearing areas in the adult [12, 31]. The condition may remain relatively mild but nevertheless distressing [32], ranging from a few but recalcitrant suppurating lesions to an advanced widespread and disabling disease lasting for years or decades. Possible consequences of long-standing, recurrent disease are multiple surgery and considerable social burden caused by chronic infection, with purulent discharge, odor, and pain [35]. In addition, there is a risk of developing a squamous cell carcinoma [9, 36, 40, 73],

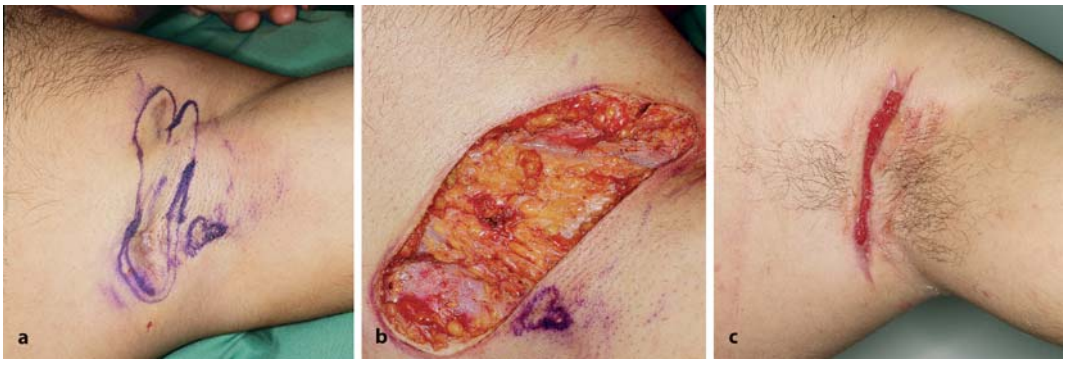

Fig. 22.1 a–c. A 30-year-old man before (**a**), directly after (**b**) scanner-assisted carbon dioxide laser vaporization of hidradenitis suppurativa of the axilla, the lesions delineated by ink, and 6 weeks later (**c**), without closure of the defect, i.e., only secondary healing

especially in the perianal region [70]. The etiology of HS is obscure.

Hyperkeratosis of the follicular infundibulum forming comedo-like impactions occludes the pilosebaceous apparatus [5, 34, 69]. This is followed by rupture of the follicular canal and the spilling of foreign-body material into connective tissue. The dumping of foreign material such as corneocytes, bacteria, sebaceous matter, and hairs into the connective tissues excites an inflammatory infiltrate. The infiltrate consists initially of granulocytes, followed by mononuclear cells, and forms a foreign-body granuloma. Epithelial strands are formed and evolve to keratin-producing sinuses lined with squamous epithelium, and fistulas and secondary comedones are typical features [5, 34, 69]. The tissue reaction is complicated by extensive inflammation and enhanced by secondary bacterial colonization and secondary bacterial infection [28, 39, 48]. This chronic inflammatory process produces richly deforming and contracting fibrotic scar tissue with subsequent functional defects [5, 34, 37, 72].

Many therapies have been tested, often frustratingly with limited or temporary results. In refractory cases surgery is essential and recommended as early as possible.

In the classic Hurley clinical grading system [29], Stage I consists of one or more abscesses with no sinus tract and cicatrization and Stage II consists of one or more widely separated recurrent abscesses, with a tract and scarring. The most severe cases (Stage III) are described as having multiple interconnected tracts and abscesses throughout the entire affected area. The Hurley grading system is very useful for overall classification of cases and may form the basis for selection of appropriate treatment in a selected anatomical region. Most patients seen in Departments of Dermatology and many of those with HS have a milder course, usually Hurley Stage II. Hurley Stage II is the commonest type of HS [35]. Milder cases may be manageable with medical therapy; Hurley Stage II cases need local surgery including carbon dioxide laser treatment with secondary intention healing (see later; Fig. 22.1). Hurley Stage III cases generally require wide surgical excisions of the entire affected region and referral to a Department of Plastic and Reconstructive Surgery.

Evaluation of the various surgical HS treatment procedures is difficult because of incomplete reporting of results and lack of controlled data. Also, the recurrence rate of certain patient material, for example troublesome cases referred to us because no successful treatments have yet been found, varies with the severity of the disease. For surgical studies double-blinded controlled investigations are not useful, and the results of individual techniques are therefore best documented through careful follow-up studies. The terms “wide” and “radical” excision are often poorly defined in published papers, and thus it is difficult to compare and evaluate the methods and results of different published series.

When the papers are written, emphasis is often placed on the technique used to cover an excision defect rather than the extent of excision or the success or failure of the treatment. The need for prolonged follow-up, even after radical surgery, is important to determine late recurrence, as local recurrence is seen for several years after surgery. Early surgical treatment is indicated when medical treatment fails and invariably when the disease is extensive. In established HS there is no evidence that treatment other than surgery has any effect on the natural story of the condition. Only wide surgical excision can cure the patient in the chronic, recurrent stage of the disease. Wide excisions, well beyond the clinical borders of activity, are mandatory, regardless of the localization of HS. The surgical methods chosen in each case depend on several factors, including the region(s) involved [6], as well as the type and severity of HS [29, 59]. Simple excisions with carbon dioxide laser [62], primary closure or exteriorization, curettage and electrocoagulation [11, 16] of the sinus tracts can be sufficient, but in cases involving the entire apocrine-gland-bearing area more extensive surgery is sometimes considered necessary [23, 58, 69, 71]. The large wounds from major excisions have either been covered by flaps or meshed grafts, or left to heal by secondary intention [2, 4, 6–8, 10, 11 13–15, 17, 19, 21, 25, 26, 27, 30, 33, 42–44, 49, 50, 52, 55–57, 60, 61, 65, 67]. In 1992, Banerjee reviewed 12 studies with a total of 284 patients, who were treated with various surgical excision methods [6]. The patients selected probably had a somewhat more aggressive clinical type than normal HS patients, since all were hospitalized for 5–42 days after surgery. The follow-up time was 1–8 years and the recurrence rate varied from 0% to 68%. It was concluded that radical excision and healing by secondary intention gave good symptomatic control in axillary, inguino-perineal and perianal regions, but was less satisfactory for the submammary location. Skin grafting and flaps should be reserved for severe recurrent disease [6]. Rompel and coworkers analyzed data from their clinic: 106 HS patients in all (61 women and 45 men) of which 61% were treated in the axillary region, 75% in the inguinal region, 16% in the genito/perianal region, and 34% in other regions [57]. In a total of 241 surgical procedures the reconstruction type was healing by secondary intention in 20%, primary suture in 41%, local flap in 11%, free skin grafts in 26%, and combinations in 1%. It seems that the patients from Rompel's center generally had less severe disease compared to the above-mentioned material reviewed by Banerjee [6], since 41% of the procedures were primary sutures. The rate of recurrence within the operated fields was 2.5%, which was not affected by choice of reconstruction method, but rather the severity of the disorder, and there were very few complications. Radical excision was suggested to be the treatment of choice and the use of intra-operative color marking of sinus tracts was reported to minimize recurrence rates [57].

Incision and drainage, performed in acute situations in various surgeries, are probably the most common treatments for HS patients, and may sometimes lead to temporary control of symptoms; however, they are best avoided since the abscesses almost inevitably recur [3, 6, 10, 55, 58]. Deroofing and exteriorization of the sinus tracts may be of value [7]. Proper exteriorization involves removal of the "roofs" of sinus tracts, removal of all granulation tissue, which in some cases may be rather extensive, and slow healing by secondary intention. It is speculated that optimal exteriorization is highly dependent on the skill and training of the surgeon, and that optimal results may therefore be easier to obtain with an excision. It is common to find large areas of skin undermined with tracks running for long distances, but usually at the same depth. Care must be taken not to create false passages. The complete roof of the track is then cut off, leaving the floor exposed. The true passages are recognizable by their well-established margins and partly epithelialized floor and walls. Care must be taken not to damage the floor of the exposed tracts. In severe cases the treatment is limited at each operating session to an extent that enables mobilization and minimizes postoperative discomfort. Sometimes this method can be used in patients whose disease is so extensive that wide excision could not be contemplated.

22.2 Methods of Closure

Several different techniques have been described, and the techniques employed include: excision and primary closure, excision followed by secondary healing, excision and split thickness skin grafting, excision and delayed grafting, and skin excision and plastic reconstruction using rotation flaps and pedicle flaps. Controversy exists about closure of the skin defect. Adequate excision will usually result in a defect that precludes primary closure, and various techniques are described to obtain skin cover, such as applying split skin grafts, transposed or pedicle flaps. Primary closure and rotation flaps, including the use of wide undermining and elliptical sutures, VY-plasty, and WY-plasty, are rarely used because of the extensive nature of the excisions; however, they usually give satisfactory results for small axillary defects, the inguinal regions, mammary folds, and the upper part of the thighs. Primary closure is reported to be more effective in axillary excisions in women because of the extra skin available in the lateral mammary area. Pollock et al. [50] have demonstrated the use of a transverse primary closure. Another possibility is a combination of primary closure and healing by granulation.

The excision defect can be left open to granulate and epithelialize. The certainty of wound healing, avoidance of a donor site, rapid mobilization with minimal discomfort, and uncomplicated management of the wound after discharge from hospital recommend its use. Healing by granulation (secondary intention) is associated with a predictable result that is as good or even superior to that obtained by skin grafting. However, complete wound closure may take up to 2–3 months. Healing by granulation is a method especially suitable for the nape of the neck and the perianum and perineum, and furthermore for controlling severe HS of the axillary and inguino-perineal areas [61, 68]. A study by Morgan et al. [44] of patients with bilateral axillary involvement compared granulation on one side with grafting on the other. Most patients preferred granulation with a silastic foam dressing. In another study, subjects reported minimal inconvenience or interruption of daily activities and minimal analgesic requirements after healing by secondary intention; wound closure was uncomplicated, with unrestrictive, stable, and cosmetically acceptable scars. As soon as patients are confident that they can handle these areas with sitz baths or compresses, as the case may be, they are discharged. To decrease healing time, free skin grafts can be secondarily applied to the granulating surface.

The principle reason for skin grafting is to prevent contracture and shorten the period of morbidity. Split-skin grafting, either immediate or delayed, has the advantage of rapid healing with complete wound healing, often in 2–3 weeks. Excision and free skin grafting is most satisfactory for shallow axillary, suprapubic, and buttock defects. For the perineum, pubis, and intercrural regions, split thickness grafts yield shortest healing times and satisfactory cosmetic results [8]. Disadvantages include an unsightly cosmetic result and the discomfort and poor cosmesis associated with the donor site [12]. In addition, the affected limb must be immobilized for several days. These can be applied immediately at the time of excision. Otherwise, a delay of 4–6 days will allow for a healthy bed of granulation tissue to form which does not bleed if the dressings are soaked off and split grafts can be applied at that time. Mustafa et al. [46] reported a preference for a 1-week delay before skin grafting to avoid missing any retained sinus tracts not completely excised. Others recommend a shorter (48–72 h) delayed skin graft to speed up the process [8]. Free grafts are complicated by the technical problems of fixation and immobilization, lengthy hospitalization, time-consuming dressings, possible partial loss, and contraction of the grafted axilla.

Excision and closure with a pedicle rotation flap or tube flap is used mainly in deep defects of the axilla [20, 27, 47, 63] and occasionally the inguinal, scrotal, and perineal regions, where vessels or vital organs may be exposed and a healthy protective covering is required immediately. The rotation of a regionally based flap is advantageous in closure when the disease process has penetrated deeply. Total excision results in an especially cavernous defect, which is likely to expose the large vessels. It is particularly ad-

vantageous in repairing the axillary wound of obese robust patients. Posteriorly based flaps are elevated from the inframammary area and rotated into the defect of the axilla [25]. The submammary donor site is closed primarily. Local flaps have been used by many for this repair. The combination of a regional flap and split thickness skin graft furnishes another means of axillary repair. Z-plasty is one of the most useful plastic surgery procedures and deserves first consideration in the prevention and contracture of scars. Generally, the length of the arms of the Z should be equal. In modified Z-plasty, first the upper and lower portions of the wound are approximated to form an elliptical central defect, which lies in the line of election. The Z-plasty is then carefully planned and the flaps developed. Free skin grafts, tubed and pedicle flaps can be used to reconstruct large deep defects of the perineum, pubis, and groin. Such flaps provide satisfactory coverage for exposed testicles and large vessels or other important structures. Rotation flaps and Z-plasty have certain disadvantages. When the axillary defect is long and wide, the arms of the Z may have to extend and disfigure the anterior chest.

22.3 Anatomical Regions Involved

The choice of surgical techniques varies according to region. Wide excision surgery gives good symptomatic control of severe HS of the axilla and perianal regions but higher recurrence rates in the inguino-perineal region and it is less satisfactory for submammary disease [63]. Despite a high recurrence rate most patients are well satisfied after inguino-perineal excision because local recurrences are trivial compared with the disease before surgery.

22.3.1 Axillary HS

Primary closure can be more effective with axillary excisions in women because of the extra skin available in the lateral mammary area. If the dissection has extended to the point where axillary vessels are exposed, this must be covered with substantial tissue, namely skin and subcutaneous tissue with its own blood supply. In cases where primary closure is not possible, rotation of a flap, usually from the chest wall, is required. The axillary region in HS is discussed more below.

22.3.2 Inguinal Disease

Higher recurrence rates are seen in the inguino-perineal region [63]. Despite a high recurrence rate most patients are well satisfied after inguino-perineal excision because local areas of recurrence are trivial compared with the disease before surgery. Excision and healing by granulation can be applied [61]. All tissue is excised down to the fascia and the wound is allowed to granulate and epithelialize spontaneously. The excision must not go deeper than the fascia, to protect the vas deferens and the testis from exposure.

22.3.3 Gluteal-Perianal-Perineal Disease

Grafting is associated with high failure rates in the perineal and perianal areas and is not advised for closure of the anal canal either. Grafts in this area may contract, leading to anal stenosis [12]. Some authors argue that cases with extensive tissue resection over the buttocks and perianal region benefit from skin grafting [8, 71], while others find that the overwhelming majority of perineal resections do well with closure by secondary intention [21]. Simple wide excision, early discharge, and home care until healing is complete minimize operative and hospitalization costs and the risk of immobilization. Complete healing requires from 2 to 5 months depending on the extent of initial disease and the surgical intervention. The patients are quite familiar with dressing techniques and therefore require little reinforcement to maintain themselves during the prolonged interval of healing. A better cosmetic result is obtained and many patients are quite concerned about the cosmetic appearance of their buttocks. Large areas will granulate in a period of several months and the patients begin to live a productive life

long before healing is complete. Digital examination of the anus and rectum should be performed in perianal HS to diagnose anal fistula [16]. The diagnosis is based on the presence of an indurate fistula in the anal canal with the primary lesion of the anal gland palpated close to the dentate line. Fistulas connecting with deep organs such as the anal canal, rectum or urethra have been rarely mentioned in the literature. Regarding perianal surgery, some authors prefer the use of a colostomy to prevent fecal contamination of the wound [71]. However, most often it is unnecessary if a thorough mechanical bowel preparation is done preoperatively, if bowel activity is suppressed postoperatively, and local hygiene is aggressive during healing.

22.4 Excision Margins

The choice of the surgical borders for radical excision is important. Usually the excision reaches the deep subcutaneous fat or the fascia. Three types of excisional limits can be discussed (after Soldin et al. [63]):

1. Limited local excision. Only the obviously diseased tissue is excised. Usually this is within the area of the hair-bearing skin.
2. Hair-bearing skin excision – the area of axillary tissue containing terminal hair is excised. The excision is performed down to the fascia.
3. Wide local excision – all hair-bearing tissue and an additional 2-cm margin of surrounding skin are removed, down to the fascia (mainly for axillary disease).

The choice of margins is very much dependent on the extent and development of HS in the individual patient. Excision of inflammatory tissue including all occluded follicles and all fistulas is mandatory, otherwise immediate recurrence will follow surgery. In cases where the disease is limited, with fistulated processes separated by healthy skin (disease Stage II according to Hurley's classification), and when most of the region is spared, excision of the skin confined to the diseased tissues is satisfactory. In cases confined to a fistulating process, it is necessary to avoid local recurrence. If any part of the fistula is left behind the inflammatory process will soon start again and often also dissect through the healthy scar and recur. In general small recurrences or new lesions seen can be excised as they occur. This will leave a lot of patients with a minor surgical scar and with fewer of the complications associated with major surgery. Even in cases where very wide excisions are performed, local recurrences or new lesions are seen and there is always a risk of new lesions in a new region. Local excision of more advanced HS (most of or the whole of a region is fistulated, Hurley Stage III) is often followed by recurrence and many authors agree that wide excision of affected skin is to be preferred. It is reasonable to excise at least all the hair-bearing skin in cases where a large area is affected. In these advanced cases most of the region is already involved by HS lesions and the aim is not to leave axillary skin that has a preponderance to develop HS lesions. Therefore, in the axilla, it is recommended to excise all of the hair-bearing skin. An extra margin of 2 cm is advocated by some authors [6, 55, 63]. In skin close to inflamed tissues an estimated free margin should be added. If radical surgery of the whole area cannot be done, the patient can still gain the relief of having a reduced disease burden following local excisions of the fistulating process. There are also cases that can be assessed as being somewhere between these two extremes. Other information about the patient's general health, surgical risks, surgical possibilities for closing specific defects and the patient's willingness to accept an unsightly scar must be balanced against the risk of recurrences. The consequences of a recurrence in the area are major surgery or a small excision.

22.5 Complications

Complications include suture dehiscence, wound separation, postoperative bleeding, hematoma, and loss of flap or skin graft. Local wound and septic infections are rare and not prevented by preoperative antibiotics. The late sequelae involve different types of problems related to scar formation, especially when in the

axilla, and on occasion require release of the contracture or even Z-plasty. In the perineum, scar contractures occur quite regularly but present little functional disability.

22.5.1 Recurrent Disease After Surgery

When single or adjacent elements are excised recurrences do occur locally even after surgery, and patients may develop new foci of HS in another region. Local recurrences may appear rapidly and in direct association with the scar, suggesting that diseased tissue was left at the time of operation, or they may appear over a longer period suggesting de novo occurrence of disease [33]. The appearance of new foci strongly suggests that the disease is of a multifocal nature. Sometimes attempts to obtain primary skin cover may lead to inadvertent compromise of the excision margin and an increased risk of recurrence.

22.6 Carbon Dioxide Laser Surgery in HS

In the early 1990s we were looking for a treatment for the most common type of HS, with a high likelihood of cure, a low recurrence rate, and one that avoided hospital admission and general anesthesia, with minimal inconvenience and time off work for the patient. One of us (J.L.) developed a modified "minimally invasive" carbon dioxide laser procedure followed by healing by secondary intention [38, 41]. There now follows a detailed description of this method.

The method involves using the simple, fast, hand-movement-controlled "paintbrush" technique and a Sharplan carbon dioxide laser (CO_2) 1030® (Laser Industries, Tel Aviv, Israel) operating at 30 W [38]. Since 1993 the method has been modified, taking advantage of the introduction of carbon dioxide laser scanners (rapid beam optomechanichal microprocessed scanner systems). From 1993 to 1994: SwiftLase® (the optomechanical flash scanner, SwiftLase, model 755, Laser Industries); from 1995 to the present day: SilkTouch® (the optomechanical flash scanner, Silktouch, model 765, Laser Industries). A focusing handpiece from a Sharplan carbon dioxide laser 1030® is attached to the miniature optomechanical flash scanner delivery system, which generates a focal spot that rapidly and homogeneously carries out a spiral scan and covers a circular area of tissue at the focal plane.

The symptomatic lesions, according to the patient's opinion regarding discharge, inflammation, infiltration or suspected abscesses, are selected for treatment. Areas that had been "silent" for more than 2 years but with signs of earlier activity, i.e., scars with postinflammatory hyperpigmentation, sometimes with dry comedones but with no actual inflammatory activity detected, are judged as "burned out" and left untreated. The diseased skin is macroscopically scrutinized for scarring, tissue distortion and discoloration, dry or suppurating sinuses, macrocomedones and other superficial signs. The examination is completed with palpation of the defects for bulky indurations and small, firm subcutaneous nodules or fluctuating purulent tissue. The selected area is ablated with the laser beam by passing it over the tissues with as much power as is controllable in the surgical situation. After wetting the surface with a 0.9% sodium chloride solution to remove devitalized tissue and drying it with a swab, the treated area can be evaluated and repeated ablations are possible in the same manner. The depth of each level of vaporization is controlled by the selection of power, focal length, scanner-controlled spot size and the velocity of the movements of the handheld scanner. We use 20–30 W, 3- to 6-mm spot size, and 12.5 or 18 cm focal length setting. The resulting depth of the vaporization procedure is determined after inspection for signs of healthy and diseased cutaneous tissue. The vaporization procedure is repeated downward and outward until fresh yellow fat tissue is exposed in the deep and relatively thin and anatomically normal skin margins laterally, with no remaining dense or discolored tissue. Usually the vaporization reaches the deep subcutaneous fat or the fascia. In the axillary region, major vessels and the nerve plexus have to be protected but this depth is seldom reached in patients with Hurley Stage II [29] HS as treated in this manner. The smaller blood vessels are readily and conve-

niently coagulated by the laser and little or no bleeding occurs during the surgical procedure. Bleeding from vessels larger than 0.5–1 mm in diameter is preferably stopped using electrocoagulation or ligation.

The treatment is terminated by a final soak with 0.9% sodium chloride solution and examination for remaining diseased areas and bleeding. The wound, left to heal by secondary intention, is immediately covered after the surgical procedure with dry dressings or ointment-impregnated dressings with an outer covering bandage attached using surgical adhesive tape, or with gauze underwear.

When patients are on acetyl salicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs) it is recommended to stop medication for 3 weeks (acetyl salicylic acid) or 1 week (NSAIDs) before surgery. No perioperative antibiotics are used. In patients with heart murmurs and prosthetic heart valves the use of preoperative antibiotics is common. In general no premedication is necessary but 10 mg diazepam orally or per rectum 1 h before surgery is used in anxious patients.

22.6.1 Anesthesia

The diseased area resulting from recurrent relapses of abscesses and chronic inflammation is delineated with ink. Following cleansing with 0.05 mg/ml chlorhexidine solution the area is anesthetized with injections of lidocaine (0.5–1.0 mg/ml) and epinephrine (Xylocaine® adrenalin, Astra, Södertälje, Sweden) with sufficient margins. Richly innervated areas, such as the groin, are pretreated with a lidocaine/prilocaine cream (EMLA®, Astra) prior to the injections. The solution is injected and infiltrates around and not directly into the affected site, forming a square around the area, thus avoiding direct contact with inflamed tissue as well as injection into the abscess itself, thereby preventing an increase of pressure and pain or eruption of purulent discharge. This procedure leads to almost complete anesthesia within 5–10 min. Recently we have started to use highly diluted local anesthetics in large volumes, the tumescens method. When larger areas require treatment, the maximal safety limit of local anesthetics should not be exceeded.

22.6.2 Postoperative Wound Care

Immediately after the wounds are surgically dressed, the patients are instructed to stand up and take a short walk. The patients remain at the clinic for 3 h following the procedure, which allows them to check for functional impairment and gives them the opportunity to empty their bowels and bladder and also to discover any bleeding before leaving. The dressings are initially left on for 2–3 days without being changed, to avoid early bleeding. Thereafter, the wound is cleansed and rinsed with tap water and the bandage changed as often as necessary, sometimes on a daily basis, until complete healing is accomplished. Since 1998 a hydrofibre dressing (Aquacel®, ConvaTec, Deeside, UK) has been used for this purpose. Usually the patient does this procedure without any need for medical professional assistance. In our experience the pain felt during wound care when changing the dressings is the most problematic event for patients in the postoperative period. In our opinion the hydrofibre bandage is less painful to remove than previously used dry dressings or ointment-impregnated dressings, although this has yet to be studied in a controlled manner. Analgesic requirements are controlled with standard doses of paracetamol. Antibiotics are used if clinical signs of secondary infection are found. The patients are followed-up for a wound check after 1 week and subsequently if there are signs of complications until they are healed; they are then followed-up at 6 weeks and at 6 months, and thereafter only when there are complications or other clinical reasons for medical intervention.

22.6.3 Practical Hints and Comments

22.6.3.1 The Carbon Dioxide Laser Technique

The poor prognosis regarding complete healing in long-standing cases of HS and the need for

prompt surgical intervention encouraged us to develop a fast and convenient surgical method suitable for an outpatient setting that was radical but at the same time tissue-sparing and that had minimally priced post-operative professional wound care. Carbon dioxide laser has previously been used in HS treatment [18, 24, 40]. Before there was access to scanner devices, we used what we called the carbon dioxide laser stripping second intention technique [38]. A carbon dioxide laser was used, operating at 30 W with a manually controlled hand piece. The beam was set to give the shortest possible exposure times with as much power as is controllable in the surgical situation, thereby causing the least lateral heat conduction and non-specific thermal injury as possible, with a narrow coagulation margin and minimal char production. If irradiation of a charred surface is continued, it will be heated to more than 400 °C, causing heat injury within the underlying tissues and margins [1, 22, 54]. Tissue vaporization by a defocused beam being moved quickly in a freehand manner in a circular motion in the "paint brush" pattern method is very dependent on the surgeon's experience.

22.6.3.2 The Use of Scanners

We use a focused continuous-wave (CW) carbon dioxide laser with a rapid beam miniature microprocessor-controlled optomechanical scanner system that moves the laser spot at constant velocity in a pattern that covers the treatment site at a dwell time of less than 1 ms. This scanner uses parallel mirrors to produce a fine spiral beam. By laying down (approximately 16–18 tracks across the entire diameter of the scanner) adjacent sets of concentric spirals, a full scan is produced in 0.2 s. An ideal way to reduce the conduction of thermal injury to the skin is to combine high fluency (energy/unit area) with a very short laser exposure time, thus obtaining the ablation of tissue with minimum thermal injury. The scanners are usually used to ablate very thin layers of skin, as in the treatment of actinic keratoses or rhytides in resurfacing procedures, with short pulses (0.2 s). Used in a continuous mode, the scanned laser beam drills downwards into the tissue and removes it in a fast, even, and fully controlled way. Before 1995 a prototype named Flashscan was used. The device worked along the same principles but used a figure-of-eight scanning pattern. It was useful, but had some shortcomings with rougher tissue surfaces and gave rise to some splashing of blood and tissues; it was subsequently exchanged for the Silktouch in 1995.

In our opinion, the laser is a suitable tool for working with the contaminated and infected tissues of HS. It has the further advantages of allowing the surgeon to kill any bacteria present (through the heat applied) and to deal with the highly inflamed and purulent tissues without touching them. The carbon dioxide laser cuts and seals small blood and lymphatic vessels. It is also advantageous in that it prevents the spread of bacteria to the surrounding tissues or bloodstream, while at the same time providing a blood-free operating field with its inherent possibilities for macroscopically examining tissue pathology. Favorable effects on the healing of experimentally infected wounds after carbon dioxide laser sterilization have previously been suggested [53, 66].

We have further developed the techniques and strategies of the carbon dioxide laser to optimize its use in the different stages of HS. Instead of using the laser as a substitute for a scalpel and cutting vertically into the surface around the diseased tissue, we start from another point. Layer by layer we vaporize the tissue from inside the central surface of the diseased area downwards and outwards until all of the macroscopically pathological tissue is removed and healthy tissue is reached. If we discover that the disease is more widespread than initially expected, the ablated area can be extended. The principle is to be as radical as possible and still save sufficient healthy tissue for the secondary healing process in order to obtain fast healing and to avoid unnecessary scarring and contraction. From our own experience of scalpel excisions of HS, initially there is an increased risk of removing unnecessary amounts of tissue, since we have to estimate how much tissue should be excised to give sufficient margins. Further, the surgical wound edges bleed a lot and are very hard to investigate for the presence of remnant pathologi-

cal tissues, which carries the inherent risk of recurrence. The carbon dioxide laser has been applied to HS by others [24] for excision use. The excision technique is mandatory when pathological anatomical examination to exclude suspected squamous cell carcinoma is indicated. It is also reasonable sometimes to debulk heavier parts of HS lesions with wide excision, to save time and reduce the amount of fumes for the vacuum filter, but as soon as the border with healthy tissues is reached, the value of treating from the inside out, starting with pathological tissue, is obvious. Every millimeter of healthy skin tissue is valuable and should be left unless there is a reason to do otherwise. The use of a scanner makes the ablation smoother and more precise, enabling the early recognition of healthy or vascular tissue and the avoidance of unintentional damage. Special caution is recommended in patients with a low ratio of diseased skin to healthy subcutaneous tissue underlying the lesions, and in those in whom the procedure is limited by muscular fascias or vital parts other than subcutaneous fat, i.e., nerves, blood vessels. The laser optical density used for treatment is considerably higher than the threshold for vaporization without residual carbon char and it generates a clean, almost char-free crater in the tissue [64]. The scanners used with a continuous emission mode give a faster, safer and more even ablation with less bleeding and better visualization of HS macropathology during surgery compared to the freehand surgical technique. During the laser treatment the endpoint is healthy tissue in all directions. The hypothesis behind the surgical method is that, by radically removing and vaporizing the macroscopically active HS disease, tissue recurrences are avoided. Actually one is tempted to speculate that it is the cause of inflammation that is the target of laser vaporization: perhaps the cause of inflammation is destroyed along with the hypertrophically deformed follicle and its content of foreign material such as keratin from corneocytes and debris from hair and bacteria. Hypothetically the sources of recurrence are the epithelial sinuses that line this debris, as they produce keratin and harbor bacteria that have the potential to be pathogenic in this environment. According to this hypothesis the surrounding inflammation is secondary and reactive to this foreign body material and not the cause of the recurrence.

22.6.3.3 How Radical Should the Therapy Be?

The target area for surgery should be diseased and damaged skin but nothing beyond the actively diseased area [61, 72]. A study of the extent of surgery and the recurrence rate of HS by Ritz in 1998 [55] and an extensive review by Banerjee in 1992 [6] give a helpful picture of the problems and complexity involved in comparative assessments of surgery in HS. The majority of patients seen in dermatology units and the majority of patients with HS have a relatively mild disease course and most often are at Hurley Stage II [29], i.e., recurrent abscesses with tract formation and cicatrization, and single or multiple widely separated lesions that have not yet turned into the more advanced stage of disease. These patients cannot be considered as candidates for advanced major plastic surgery, but still suffer from a chronic and disabling disease [35]. New abscesses outside the clinically symptomatic skin area cannot be prevented by any known surgical method and they should be regarded as an indicator of underlying disease activity rather than as a shortcoming of the surgical method [6]. Our patients are predominantly women and that may be a reflection of the fact that the disease more often presents in otherwise healthy females during their fertile years, especially the inguinal and genito-perineal forms [32, 45, 46, 51]. Surgery alone is only permanently curative in a select group of patients, and only temporarily in others. The results of our method accord well with results from other types of surgery [6, 25] and the need for repeated treatment sessions should be considered. This method is conveniently repeated, and as it is tissue-sparing the risk of contractures is reduced. In recurrent disease after carbon dioxide laser surgery, repeated carbon dioxide laser surgery in conjunction with supplementary medications, such as long-term immunological modulating antibiotics, e.g., tetracyclines, retinoids or cyproterone acetate

combination medication, should be considered. The largest group of HS patients, i.e., the early cases or the cases of mild to moderate severity, probably suffer a lot from their disease despite their relatively limited symptoms. For both economic and practical reasons, in clinical practice there is a tendency for surgery to be withheld except for the most advanced cases. The patients we have shown to gain considerably from laser surgery in our clinic had previously been treated conservatively. There are reasons to believe that our method will prove to be an adequate surgical choice for early surgical treatment and a study of carbon dioxide laser treatment of early HS lesions is in progress.

The better safety and accuracy that come with the use of microprocessor-controlled scanners make this technique available for more general use and enable it to be used in other areas of treatment for HS patients, i.e., dermatologic surgeons, general and plastic surgeons, and gynecologists. It will be possible to treat lesions completely and radically very early on in the course of the disease, i.e., the acute primary HS, and this could be done in outpatients with the wound left to heal by secondary intention rather than the current option of ineffective incision and subsequent expensive wound care with painful tamponade. Some of our chronic patients would be much better off under this type of regime.

22.6.3.4 Concluding Remarks

No exact estimates of the costs have been made but, but there are at least three reasons why carbon dioxide laser is less expensive than traditional excisional surgery. Firstly, the total operation time is shorter, which keeps the need for qualified personnel to a minimum, and permits a more rational use of room facilities. Secondly, there is no need for nursing assistance postoperatively. Thirdly, the postoperative symptoms are less and fewer patients have to refrain from work. A more detailed cost–benefit analysis of this method remains to be done. The patients we selected were at Hurley Stage II, which we predefined as operable by our method. Patients classified as Hurley Stage III were referred for wide excision and reconstructive surgery. Our impression is that the most common form of HS is Hurley Stage II and that most patients seem to stay at this stage without progressing to Hurley Stage III. When patients were thought to be suitable for surgery they were operated on at our clinic and a few were referred for wide excision surgery.

In conclusion, for patients with HS, modified minimally invasive carbon dioxide laser treatment is a safe, simple, fast and economical surgical method with satisfactory cosmetic and functional results that is suitable for the outpatient setting. The use of carbon dioxide laser microprocessor-controlled scanner devices has made the technique safer and less surgeon dependent. The technique allows early and simple treatment of HS lesions that previously perhaps tended to be left to less effective, local and conservative remedies.

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Chapter 23

Radiation Therapy

Renato G. Panizzon

23

Key points

- Radiation therapy is an option for recalcitrant disease
- Even a minute dosage appears to have a clinical effect
- In chronic disease higher doses are used
- The majority of patients in the published case series have had beneficial effects from radiation therapy
- The total dose should not exceed 12 Gy
- An interdisciplinary approach to radiotherapy is recommended and should include a dermatologist with radiotherapy experience

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23.1 Introduction

There is a revival of interest in the use of radiotherapy for benign skin diseases and among these for hidradenitis suppurativa (HS) even though we do not consider radiotherapy to be the treatment of first choice. It can be a supportive measure, especially in cases difficult to treat. In order to promote evidence-based practice, we have to search through the data from several decades to find enough on HS (Table 23.1).

Table 23.1. Evidence-based literature review

Reference	Year	Cases
Rütz (in [8])	1925	60
Heidenhain (in [8])	1926	46
Sulger (in [8])	1930	82
Tachau (in [8])	1934	25
Erikson (in [8])	1942	225
Cocchi (in [8])	1943	295
Pulvermacher (in [8])	1948	82
Lange-Hansen (in [8])	1949	375
Lyndrup-Krause (in [8])	1949	60
Hess (in [8])	1949	660
Eilermann (in [8])	1949	50
Pape and Gölles [1]	1950	142
Strauss (in [8])	1951	132
Glauner (in [8])	1951	215
Dornuf and Schönwald (in [8])	1951	300
Buchtala and Viehweger [2]	1952	100
Müller and Sittig (in [8])	1955	42
Fischer [3]	1957	12
Seegenschmiedt et al. [6]	2000	221
Fröhlich et al. [5]	2000	231

23.2 Treatment Regimens

In general, the earlier the treatment begins, the better the outcome.

Another aspect of the treatment regimen to consider is the dose, which ideally should be as small as possible [1, 2] for the acute stage of HS. Fischer [3] called this "Röntgenkleinstdosen" ("very small Röntgen dose"), namely a treatment schedule in which only 0.05- to 0.2-Gy single doses are used. The total doses of these series amount to between 1 and 4 Gy. If the HS is chronic and recurrent, the success rate is not as good, and higher single doses of between 0.5 and 1 Gy have to be applied [4] (Table 23.2). In the case of chronic disease treated with the aforementioned doses, the recurrence rate is at least 38%, whereas with the early application of very small doses, the rate is only 19% [1]. Radiation therapy can be adapted easily to the depth of the lesion between 5 and 30 mm, and this is calculated using the "half value depth" (HVD). Machines that deliver the treatment are mostly of the superficial X-ray type with a radiation quality of 20–150 kV. The irradiation field is chosen to be as large as possible. In recurrent cases, two or more series may be applied, but a total dose of 12 Gy should not be surpassed.

Table 23.2. Practical guidelines: recommended dose schedule for the treatment of hidradenitis suppurativa. Radiation quality (kV and filter) depend on the depth of hidradenitis suppurativa

Stage	Single dose	Fractions	Frequency
Acute stage	0.2 Gy	4–12	Daily
Recurrent stage	1.0 Gy	4–12	3 times per week

23.3 Case Series Reports

Fröhlich et al. [5] examined 231 patients and found complete relief of symptoms in 89 patients (38%); in 92 patients (40%) there was clear improvement and only 2 patients did not react to radiotherapy. No side-effects were noted.

In the same year Seegenschmiedt et al. [6] examined patients treated with radiotherapy for benign diseases; among them were 221 HS patients. They found significant geographic and institutional variations in the treatment schedules. The doses prescribed were mostly in the low dose range and the treatments were mostly carried out by radiation oncologists. There was a decrease of orthovoltage units and a demand for more mega voltage units, which compromises the treatment's cost-effectiveness. Side-effects with this treatment modality are very rare, especially if the dose schedules are carefully followed. Even after several series of treatments the total dose per lifetime per field should not exceed 12 Gy.

23.4 Conclusion

In all cases we recommend an interdisciplinary approach [7] in order to offer our patients the best possible and customized treatment for this debilitating disease.

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Chapter 24

Experimental Physical Therapies

24

Gregor B.E. Jemec

Key points

- Depilation may prove to be a useful adjunct therapy
- New physical therapies should be tissue conserving
- New therapies should be tested in a standardized and clinically significant manner

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24.1 Introduction

Whenever there is more than one therapy available for a particular ailment, it is often suspected that none of them is universally effective. There is definitely scope for improving the physical and surgical methods for treating hidradenitis suppurativa (HS). The rationale for physical therapies in the later stages of disease is strong. After the formation of sinus tracts it is unlikely that pharmacological treatment can achieve the desired therapeutic effect, unless specific biological targets can be found in the epithelial tissue lining the sinus tracts. The treatment options for Hurley Stage III and unresponsive Stage II disease are therefore currently restricted to physical destruction of the diseased tissue using different treatment modalities [1]. A series of physical therapies have been suggested (see Table 24.1).

24.2 Photodynamic Therapy

Photodynamic therapy (PDT) provides semi-selective tissue destruction and a general antimicrobial effect. It is currently used extensively for the treatment of precancerous lesions or non-melanoma skin cancer [2]. The treatment is based on the activation of a photosensitizer applied to the tissue (usually absorbed through the skin surface), and subsequent tissue destruction. The photosensitizer most commonly used at the time of writing is either aminolevulinic acid (ALA, 20% cream) or esterified aminolevulinic acid. Other photosensitizers are available for intravesical therapy, for example, but their effects on skin diseases are as yet unproven. Similarly, potential photosensitizers, such as methylene blue, are limited in their effects to being antimicrobial. ALA can be purchased from a supplier of analytic substances, or bought as one of two commercially available products (Metvix®, Photocure, Norway or Levulan®, Dusa Pharmaceuicals, USA).

It has been shown that ALA penetrates the skin and is absorbed, theoretically allowing it to reach superficial lesions of HS. Following absorption of the substance it is metabolized along the heme pathway to protoporphyrin IX, which

Table 24.1. Experimental physical therapies in hidradenitis suppurativa (*HS*)

	Treatment	Patients	Location	Treatment	Follow-up	Effect	Complications	Reference
1	PDT	Four women, aged 19–46 years	One axillary, one axillary and inguinal areas, two inguinal areas	20% 5-ALA for 15–30 min, followed by blue light, 1- to 2-week intervals; three to four treatments	3 months	Three patients: 75% improvement; one patient: 100% improvement	None	[5]
2	PDT	Four patients	Three axillary disease, one groin disease	20% 5-ALA for 4 h, followed by 533 nm laser or 570–670 nm broad band light giving 15 J/cm^2 once weekly for 3 weeks	8 weeks	No significant improvement	One dropout because of discomfort, one experienced worsening	[6]
3	Cryotherapy	Ten women, aged 24–45 years	Three axillary, one breast, four groin, one axillary and groin, one all three sites	Cryotherapy using liquid nitrogen to freeze single nodules to a core temperature of –20 °C	Not stated clearly, but apparently up to 6 weeks (end of healing)	Four marked improvement, four improvement, two no response	Average healing time 25 days, 6/10 experienced postoperative infection, two experienced ulceration, three graded pain during healing as maximum on a 1–4 score	[13]

is a potent photosensitizer. The process occurs naturally as the main pathogenic process in porphyria. In healthy tissue the protoporphyrin IX is further metabolized by the enzyme ferrochelatase to non-phototoxic substances. In metaplastic or neoplastic tissue the activity of ferrochelatase is lower than that in healthy tissue, and a semi-selective accumulation of photosensitizer therefore occurs, which allows more targeted destruction of the metaplastic or neoplastic tissue.

PDT has recently been tested in a number of non-neoplastic diseases. These include acne rosacea [3], acne vulgaris [4] and HS [5, 6] (see Table 24.1). For HS two studies have been published. The first study, by Gold et al. [5], describes four cases treated with PDT (Levulan® and blue light). Only a short incubation period was used, and the treatment was repeated three to four times. No co-morbidity was reported, and at follow-up 3 months afterwards all cases had improved 75–100%, suggesting that the treatment may be of benefit. The exact outcome variables were not stated, e.g., VAS scores or Sartorius scores. The study is interesting but not well documented, and the inclusion criteria open the possibility that simple furunculosis rather than HS was treated. In a subsequent series of cases Strauss et al. [6] described four patients treated with generic 20% ALA and either 633 nm laser or a 570–670 nm broad band light source without significant effect. A longer incubation time and better case definition were used. Furthermore the use of red light allows deeper penetration of the light energy and therefore this is theoretically more suitable for the treatment of HS. The author's limited experience is in better accordance with the latter report than with the former. For HS the lesions treated most successfully have apparently been those of

Stage I disease, suggesting that sinus tracts are not affected and that either the inflammatory process itself or pro-inflammatory substances are targeted.

The mechanisms by which PDT affects these diseases is not known, but it has been suggested to be via tissue destruction of, for example, hyperplastic infundibular epithelium in acne, or by a simple antibacterial effect analogous to the use of blue light in acne. Additional practical problems are however involved in the use of PDT for HS. It is well established that up to one-third of all PDT patients experience considerable pain during illumination. In the study by Strauss et al. [6] one of four patients dropped out due to pain and discomfort. This appears to be particularly associated with larger areas being treated, and with the sensitivity of the areas, e.g., it is usually worse on the nose than on the back. Even if PDT is found to be effective, this factor may prove to be significantly restrictive for the use of PDT in HS.

The discrepancy between the results observed strongly suggests the need for a controlled trial, and may be due to the stringency of inclusion criteria, variation in the stage of HS being treated, and a number of other factors.

24.3 Depilation

Theoretically depilation could offer some relief to patients with HS. Previously X-ray therapy has been used to treat HS [7, 8]. The dosage varied, but often successful therapy induced depilation of the treated areas. Earlier papers on the topic have suggested that the positive effects were due as much to depilation as to the anti-inflammatory effects of the treatment (Chap. 23).

Such an effect may be hypothesized from the histology of the early lesions. An element of follicular occlusion is found in early lesions, and although pharmacological treatment with retinoids, for example, has been disappointing in most cases, the physical removal of an obstructing hair shaft may prove even better at draining the follicle. Furthermore, free hair fragments may on occasion be found in lesions, suggesting that they may help to maintain the lesions by acting as foreign objects and evoking a chronic inflammatory response with, among others, multinucleated giant cells [9]. Removal of hairs may therefore not only aid drainage, but also remove the necessary seeds for perpetuation of established lesions.

Depilation has however traditionally been suspected as a possible causative factor in HS, but the pattern of use of cosmetic procedures in the areas predisposed to HS does not appear to be different in patients and healthy controls [10, 11]. Furthermore, many patients with HS have never used depilatories in the areas where lesions occur. This makes it unlikely that any depilatory procedure forms a significant etiological factor in the development of HS.

In general, laser depilation has been shown to be a useful technique for hirsute patients, apparently using any of several types of available lasers. The absorption of laser light in the hair follicle induces transition to a telogen phase, and apparently shortens subsequent anagen phases of the follicle, consequently resulting in the growth of a shorter and thinner hair shaft [12].

Several unpublished cases among the authors of this book appear to substantiate this claim, although the success rate and duration of any beneficial effect are not known. Some patients apparently experience long-lasting remission, whereas others only have shorter periods of relief. Based on the available information, laser depilation nevertheless appears to be a promising area for further studies.

24.4 Cryosurgery

Cryosurgery has been used extensively in the treatment of both benign and malignant skin tumors. Usually liquid nitrogen is used as the coolant, and the effect of the cryotherapy is to induce necrosis based on hypothermic damage of both cell membrane and cytoplasmic organelles.

A study reporting the follow-up of ten patients treated with cryotherapy has been published suggesting that cryotherapy is a feasible form of therapy in select HS cases [13]. The treatment is however not unproblematic, and

several and considerable practical restraints exist. The treatment is associated with additional pain, which is already a dominant clinical problem to HS patients. Additional iatrogenic pain is therefore an a priori drawback of the method. A significant proportion of the cases published furthermore experienced complications with postoperative infection. Finally, cryotherapy is a destructive process and commonly associated with a long healing time. In the published study [13] the healing time was on average 25 days. On the whole cryotherapy does therefore not appear to hold any clinically significant advantages over other forms of physical therapy. Theoretically a more precise delivery of the cryotherapy could overcome some of these drawbacks, but would also obliterate the immediate practical benefits of the method, namely being fast and easy.

24.5 Discussion

Physical therapies may be directed against either the secondary prevention of early lesions or the destruction of established lesions. For true primary prevention of early lesions the pathogenic process is insufficiently described to allow a causal therapy, although the use of laser depilation may yet prove to be fruitful in proper studies. The possible effect of PDT on the hair follicle is at present unclear. It is not convincingly proven that the penetration of ALA-PDT is sufficiently deep to allow treatment of established lesions of Hurley category II or III. Nor is it established that ALA-PDT has any effect on sinus tracts. The effects may therefore be more in line with the effects of this treatment in acne vulgaris, where a significant clinical effect has been shown in some studies. ALA-PDT is however associated with considerable post-treatment pain and inflammation in acne patients and this may also limit its use in HS.

These reservations however stem partly from the paucity of data, and partly from the practical consideration of penetration. It is entirely conceivable that the photosensitizers used do not penetrate the tissue sufficiently because of their formulation. A more liquid preparation may allow deeper penetration of the photosensitizer into the hair follicles. The use of red light is theoretically sufficient, but even here there is room to improve the scope of this modality. In general the paucity of data requires additional well-designed studies, which should initially be relatively small, strongly structured proof-of-concept studies. With current technology the justification of an actual randomized controlled trial is debateable.

Destructive methods have to respect the general surgical principle of tissue conservation, i.e., that healthy tissue should be left intact. In HS sinus tracts normally occur under healthy skin which need not be destroyed. Precision in the application of destructive methods is therefore very important. While indiscriminately destructive methods such as cryotherapy, and probably also electrodesiccation, may be expected to work, they also induce unacceptable collateral damage. In addition unnecessary tissue destruction induces significant iatrogenic morbidity in the patients, as the lesions are often slow to heal, are susceptible to suprainfection and cause additional scarring. With improved imaging techniques and more targeted delivery of treatment this could be overcome to some degree, but is unlikely to be removed altogether.

A number of hypothetical and speculative physical approaches may be imagined. Improved lesion imaging may for instance also allow future intralesional therapies with application of light or pharmaceutical substances directly into the lumen of the lesion. Similarly, radiofrequency devices may provide relief via an effect on the connective tissue surrounding the lesions. Finally, UVA1 therapy may provide an anti-inflammatory effect as well as scar reduction if applied locally. It is most likely that the potential of a series of novel physical therapies will be explored over the coming years.

24.6 Practical Guidelines for Testing New Physical Therapies

The option of randomized controlled trials is generally not available for surgical techniques. In lieu of the randomized controlled trial a lower degree of evidence is therefore acceptable. The

key features of any investigations should remain the randomization, which has independent value even when assessed in an open or a single-blinded fashion. The central problem is one of control, but in an exploratory period abstention from active treatment is enough. In future cases sham procedures may be carried out when possible, providing there are objective documentation and an adequate follow-up. There must be randomization of both patients and lesions to prevent bias. Follow-up should be for a minimum of 3–6 months and it is advisable to include both patient-centered subjective methods of assessment as well as more objective methods. Subjective methods can include health-related quality of life questionnaires developed for skin diseases, e.g., DLQI or Skindex [14, 15], and VAS scores of pain and disease severity. Objective quantification may include standardized clinical scores such as the Sartorius score [16], ultrasound imaging and photography.

For bilateral HS lesions randomized intra-individual left to right comparisons of physical therapies are possible. However it is not advised to compare lesions in different regions directly, for example axillary and genitofemoral lesions; this is because the results of therapy often indicate different regional susceptibility in patients, possibly because of differing shear forces and other local phenomena. Study requirements are summarized in Table 24.2. Early exploratory studies should similarly be aimed at providing the necessary data for the planning of larger controlled and randomized studies, and should therefore preferably use the same outcome variables.

Table 24.2. Factors to consider when planning experimental studies of physical therapies. Controls are essential and should be set up for each lesion and for the patient. Inguinal lesions are not appropriate controls for axillary lesions. (*DLQI* Dermatology Life Quality Index, *IPL* intense pulsed light)

Element of study	Example
Classification and characterization of cases	Hurley classification
Randomization of patients and lesions	Flipping coins or drawing lots
Outcome variables defined	Should include subjective, e.g., DLQI, and objective, e.g., Sartorius score, elements
Standardization of therapy	Depilation using a IPL device at a specific setting for a set number of treatments
Follow-up	Minimum 3 months, and preferably longer

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Chapter 25

Treatment

Gregor B.E. Jemec, Jean Revuz

25

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25.1 Introduction

The current requirements of evidence-based medicine find little support in the existing literature on the treatment of hidradenitis suppurativa (HS). Very few randomized controlled trials have been performed, and where this has happened the trials are small with a weak predictive value. The existing literature is mostly based on cases and case series, and in an effort to strengthen these we have asked for expert evaluations in the previous chapters of this book. This should however not stimulate therapeutic nihilism! Expert assessment combines anecdotal evidence and personal experience to suggest possible approaches to therapy, but this needs to be supplemented with formal structured studies. Nevertheless, it is possible to suggest a strategy for the treatment of HS based on existing knowledge.

25.2 Staging the Disease

Treatment of any disease should be graduated to reflect disease intensity. For HS this means that staging according to Hurley's criteria is beneficial and should be done prior to therapy (see Table 25.1). It is however important to realize that disease evolution in individual patients is not simply linear, and that the stages imply different needs and therapeutic opportunities because of the predominant features of each stage, e.g., scarring in Stage III (see Fig. 25.1). Of all patients, it is estimated that as many as 75% remain in Hurley Stage I, 24% progress to Hurley Stage II and only a small minority progress further. In addition to the staging of the disease it is mandatory to obtain information about the frequency of flares before the start of therapy. The use of the lesional score of Sartorius (see Chap. 3) and the counting up of the number of painful days and of the intensity of pain may be very helpful for that purpose.

Table 25.1. Hurley's criteria for staging hidradenitis suppurativa (*HS*)

Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization
Stage II: Recurrent abscesses with tract formation and cicatrization Single or multiple, widely separated lesions
Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area

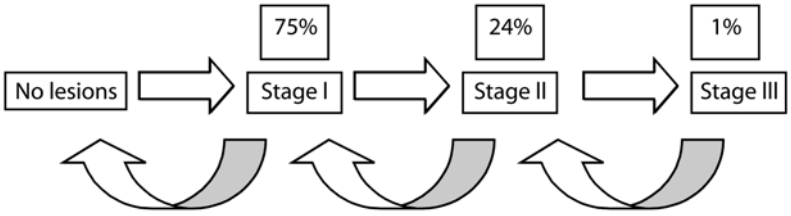

Fig. 25.1. Prevalence and strategies for therapy

The goal of treatment is to reduce the extent and progression of the disease so as to bring the patient back to a milder stage (see Fig. 25.1).

25.3 Treatment of Hidradenitis Suppurativa Hurley Stage I

This most limited form of disease is the most amenable to medical therapy, and can often be held in check by prophylactic treatment. In Stage I disease the patients often have only a few flares per year. Treatment is therefore most often aimed at reducing the duration of the flares (Table 25.2), and may consist of:

- Topical clindamycin 1–2%.
- A short course of systemic antibiotics (7–10 days). A large number of various antibiotics have been tried in this situation. The patient's previous experience may help the choice.
- Resorcinol.
- Intralesional steroids.

Such a treatment aimed at shortening the duration of a flare cannot be effective unless it is given very early, i.e., within hours of the first symptoms of a new flare. In the case of a short course of systemic antibiotics, that means that the patient has to keep the drug with him/her and use it before seeing the doctor. In the case of intralesional steroids the specialist has to be reached in an emergency.

If flares are more frequent most patients benefit from adjuvant preventive therapy, which may include azelaic acid applied daily. For this group of patients prophylactic therapy combined with treatment of flares may allow them to gain control of their disease, and in some cases the routine use of adjuvant preventive therapy alone may suffice to control the disease. For patients with frequent (one per month or more) and severe flares, treatment should however be intensified to the level required for Stage II disease (see Table 25.3).

Table 25.2. Treatment of HS Hurley Stage I disease

Topical treatment:
Clindamycin 1% (lotion)
Clindamycin 2% (cream)
Resorcinol
Short course systemic treatment:
Tetracycline
Erythromycin or other macrolides
Amoxicillin + clavulanic acid
Clindamycin
Others
Adjuvant preventive therapy:
Azelaic acid
Zinc gluconate

25.4 Treatment of Hidradenitis Suppurativa Hurley Stage II

Patients seen at the specialist level are frequently Stage II patients. The treatment aims to cure these patients or at least reduce them to Stage I disease. The presence of sinus tracts and scarring requires a combined treatment involving both medical and surgical therapies. The balance between the two depends on the amount of scarring and permanent suppuration present. The medical therapy aims to control acute inflammation and may also be used to prepare the patient for surgery.

For patients with little scarring and much inflammation, intensive, long-term antibiotic therapy with systemic clindamycin and rifam-

Table 25.3. Treatment of HS Hurley Stage II

Medical treatment (systemic only):
Clindamycin + rifampicin
Dapsone
Systemic adjuvant or maintenance therapy:
Zinc gluconate
Tetracyclines
Surgical treatment:
Exteriorization
Local excision
Laser evaporation

Table 25.4. Treatment of HS Hurley Stage III. (*TNF* Tumor necrosis factor)

Medical treatment (palliative):
Corticosteroids
Ciclosporin
Methotrexate
TNF-alpha inhibitors
Surgical treatment:
Wide excisions
Radiation therapy?

picin is recommended. Treatment should last for 3 months. If pain, suppuration and frequency of flares are reduced to an acceptable level, a maintenance treatment with tetracyclines or high-dosage zinc or dapsone may offer long remissions. In some patients the level of improvement is so high as to permit the use of Stage I therapy, i.e., therapy of flares only.

For patients with scarring and sinus tracts the medical treatment should always be supplemented with local surgery, either using cold steel or laser evaporation. In milder cases exteriorization of sinus tracts may suffice, whereas actual excisions may be necessary for larger lesions. Limited excisions are particularly useful when an abscess-sinus tract recurs frequently with flares at the same location. This kind of limited surgery may be performed in the outpatient setting with local anaesthesia and is well accepted by the patients who are frequently reluctant to have major excisions. On the other hand, general experience shows that the larger the excision, the lower the potential for recurrence. So a balance between the advantages and drawbacks of the two approaches has to be weighed up by the patient (see Table 25.3).

25.5 Treatment of Hidradenitis Suppurativa Hurley Stage III

No curative effect can be expected with medical therapy in Stage III disease. All medical therapy therefore aims to be palliative and temporary, i.e., the disease recurs shortly after the treatment is stopped. The antibiotic combination of clindamycin and rifampicin may also be helpful.

An alternative viable strategy for gaining better control of the disease at this stage may be an immunosuppressive therapy. Traditionally corticosteroids and ciclosporin have been used. Recently the use of tumour necrosis factor alpha (TNF-alpha) inhibitors has been suggested by several authors (see Chap. 20), and randomized studies may confirm these observations in the future. Currently this therapy should be seen as experimental.

At this stage, however, the only possibilities for curative treatment are extensive surgery and radiation therapy, if one is not afraid of the risk of cancer promotion (see Table 25.4). Healing by secondary intention has generally been advocated, although this extends the postoperative need for additional nursing and wound care. In general, postoperative scarring is less of a problem than scarring from the disease itself.

25.6 Hidradenitis Suppurativa with Cysts

Occasionally HS may be associated with multiple large cysts generally involving flexural areas. In this case treatment may be attempted with acitretin. Isotretinoin appears to be less effective in this rare form of HS as well. Excision of multiple cysts is bothersome but may be more effective on the long term. This subtype should not be confused with steatocystoma multiplex.

25.7 Experimental Therapies

HS is not an easy disease to treat. Often standard therapies fail, and both patient and physician are left with a therapeutic challenge. Most often one of two general approaches is used in off-label/experimental therapy. One avenue of approach is to regard the disease as a predominantly inflammatory disease, and consequently treat with immunosuppressive drugs as in so many other dermatological diseases. The use of topical immunosuppressants is rarely sufficient, and systemic therapy has been tried with corticosteroids, ciclosporin, methotrexate, dapsone and TNF-alpha inhibitors. All these treatments require special precautions, but may be useful for gaining control over an otherwise debilitating disease.

The other avenue of approach is to regard the presence of microbes as the primary pathogenic event and treat heavily with antibiotics. Most available antibiotics have been used to varying effect in individual cases.

25.8 General Requirements for Treatment

The difficulties of treatment mean that there is a strong need for additional randomized controlled trials in HS therapy. Such trials however require data for planning, and any successful treatment regimens should therefore be reported. This requires individual physicians to keep a strict log of standardized outcomes, i.e. Sartorius score, pain VAS, number of flares, etc. in order to enumerate the results obtained. With improved reporting sufficient data may become available for a better assessment of the relative value of various experimental therapies.

Chapter 26

Hidradenitis Suppurativa – Patients' Frequently Asked Questions

26

Jean Revuz

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26.1 General Questions

1. Which doctor should I see?
Depending on the severity of the disease it could be a dermatologist, a plastic surgeon or a proctologist. What is important is that the doctor knows about hidradenitis suppurativa (HS).

2. Is it a rare disease?
No, it affects an estimated 1% of the population. It is therefore a relatively frequent disease, but it is often not diagnosed. Many patients do not know what they have and are only told of their correct diagnosis after many years.

3. How do I distinguish between a simple boil and HS?
The location (groin and armpits), and the chronicity of the flares are important guidelines. That is to say, if a patient with HS has a lesion outside the predilection areas it is impossible to tell the difference.

4. Where can it develop?
Essentially in the armpits, between and under the breasts and the groin. It may also involve the glueal cleft and the perineum, and in some cases the entire ano-perineal-inguinal region. In rare cases it can involve buttocks, ears and other regions.

5. Can it affect the face?
No, except if it is associated with acne, which is not very frequent.

6. Is it a contagious disease?
No.

7. Does it get worse with time?
One cannot say. Generally it is considered to be worst during the first few years, but there are exceptions to this.

8. Can you die from it?
No, except in very rare cases if cancer develops in one of the lesions and is not treated early enough. Historically amyloidosis has been described in untreated but chronically infected patients; but this probably no longer occurs.

9. What are the stages of the disease?
Hurley's classification is used to classify the stages of the disease. Stage I is characterized by lesions, flares and sinus tracts that are separated from each other. In Stage II the flares are linked to each other by tunnels and/or by excessive development of thickened (hypertrophic) scar tissue. Stage III is characterized by the development of a large area of suppurating (oozing), fibrous tissue. In Stage III, surgery is the only effective treatment.

10. Is it necessary to operate when the first symptoms of the disease are diagnosed?
If the patient is suffering from inflamed lesions without chronic suppuration and without thick scar (hypertrophic) tissue, and especially in the case of a single lesion, it is best to try medical treatment. But surgery may be necessary in the early stages: an incision in a boil may be the only way to relieve the pain and empty it of pus, but the effect is short-lived and we do not recommend the procedure; the surgical removal of a single but chronic boil, or recurrent nodule in the same place, is an effective form of early treatment.

11. Why after surgery do I see new lesions appear in new areas?
New lesions appear after excision, but one can also see them appear in the absence of surgical treatment. The appearance of new lesions in new areas does not depend on whether or not surgery has taken place.

12. Can this disease be sexually transmitted?
No.

13. Is this an autoimmune disease?
In all probability not.

14. Is it a disease due to a hospital infection?
No.

26.2 Heredity

1. Is this an inheritable disease?
Partly. In about one-third of cases there is someone in the family who is affected by the disease.

2. What are the risks of transmitting the disease to my children?
There is little risk, but it is difficult to calculate. The risk is probably greater if there are other cases in the family, but the possible degree of severity cannot be predicted on the basis of your own experience.

3. Has a gene responsible for the disease been found?
No.

4. Can you screen for the disease?
No.

26.3 Pregnancy

1. How does the illness develop during pregnancy?
There is often an improvement during pregnancy, but this is not always the case.

2. Is there a risk to the baby during birth?
The risk is practically nonexistent. There may be a risk of bacterial infection if there is serious and persistent suppuration at the time of delivery. But in this case a caesarean delivery is always an option, or otherwise it is possible to prevent the infection of the child with antibiotics. In any event there is no serious risk.

3. Is it possible to breast-feed the baby? Isn't there a risk that the disease can appear in the region of the breasts?
It is perfectly all right to breast-feed. There is no reason why this should provoke an outbreak of lesions in the region of the breasts.

4. Is sterilization advisable?
No.

5. Is the disease related to hormonal abnormality (irregularity?)
No.

6. What type of contraceptive pill is best-suited if one has this disease?
In some cases treatment with very big doses of cyproterone acetate (Androcur 100/mg per day) leads to an improvement, but firstly these cases are rare and secondly it is difficult for the patient to tolerate heavy doses for very long. The use of the pill Diane® (which contains 2 mg cyproterone acetate) is felt to be beneficial by some women: there is no harm in trying. As a general rule, however, the fact that you have HS should not affect your choice of pill.

7. Does the disease disappear with the menopause?
Normally it does, but there is no guarantee.

26.4 Treatment

1. Is there one particular treatment that is successful?
No.

2. Should I take anti-inflammatory drugs?
Anti-inflammatory drugs may reduce pain in the short term: there are no indications to the contrary. Their only benefit is to relieve pain. They are sometimes suspected of encouraging the spread of, or aggravating, infections, but this has never been convincingly demonstrated. However, it is advisable to be careful.

3. Can I use Roaccutane®?
Isotretinoin (Roaccutane®, Curacne) is almost never effective. One can try retinoids for patients who also suffer from severe acne, but (a) these cases are rare and (b) one usually sees an improvement in the acne, but not in the HS.

4. When suppuration is permanent, can I take antibiotics? And for how long?
Antibiotics are sometimes useful. They can stop suppuration, deter an inflammatory growth and make it less painful, but this is not always the case. Each patient must try them for him or herself. An antibiotic that targets a bacteria identified by bacterial analysis can be used, but this is not obligatory. When there is permanent suppuration, surgery must be considered.

5. How can I relieve itching?
Itching is frequently a secondary effect of using local remedies or deodorants, antiseptics or other remedies. It is best to stop using them if they are doing little or no good. Chronic suppuration is the other factor involved in itching, and this takes us back to the problem of treatment to stop chronic suppuration.

6. What kinds of analgesic should I use? Should I use them for long periods?
Analgesics are not very effective against pain from inflammation. The essential thing therefore is to try to fight the infectious inflammation itself. However, all analgesics can be used.

7. What does treatment by laser consist of?
There are at least three types of laser that can be used:

a. The CO_2 laser is used for surgery under a general anesthetic in place of surgery using the scalpel. The advantages of this type of intervention are dubious; it is up to the surgeon to decide.
b. Lasers used for the removal of hair have been tried in some cases. It is too early to say whether this has an effect on the occurrence of new lesions.
c. "The smooth beam" is another technique, which seeks to destroy (sweat) sudoral and (fat) sebaceous glands without touching the surface skin. This, too, is a technique in its infancy and only at some future date shall we know whether it is of interest.

8. Does definitive depilation stop new lesions?
See Question 7.

26.5 Practical Questions

1. Can one use sanitary tampons?
Yes; HS lesions do not penetrate the vagina.

2. Should linen be washed separately?
No; this disease is not infective.

3. Is it possible to shave or remove hair by waxing?
There are no contraindications. However, some patients experience further inflammation following depilation; others benefit. You just have to try.

4. Is it better to take a bath or a shower?
It makes no difference.

5. What soap should I use: is an anti-septic soap advisable?
Any soap will do; it is not necessary to use antiseptic soap.

6. Can you catch this from a toilet seat?
No; it is not contagious.

7. How do I get rid of the smell of suppuration?
When the smell is very strong, in cases of chronic suppuration it is often because there are anaerobic germs present. These can be controlled by clindamycin or metronidazole, but in such cases surgery has to considered.

8. Can I use talcum or deodorants?
In principle, yes. Try and see how it goes.

9. Does the climate have an influence on the disease?
There is no firm evidence on this. Some patients say that they feel less well when it is very hot or very humid.

10. Should I take precautions against certain foods?
In principle, no.

26.6 Hints For Daily Life

1. How can I make the lesions mature more quickly?
When it is a case of deep lesions covered by normal skin, it is useless to hope to make the lesions mature more quickly by using alcohol-impregnated wet dressings. This may perhaps be possible with superficial dressings. In some cases an antibiotic treatment adapted to suit the case may cause the lesion to disappear, but this is far from always the case. In fact, faced with the most typical lesions – that is to say deep lesions – only an intralesional injection of corticosteroids or excision with a scalpel will relieve pain and release pus. Depending on the place, the patient, the type of lesions and their seriousness and topography, the lancing of an abscess takes place under a general or a local anesthetic, with or without hospitalization.

2. Can I try to drain an abscess myself, without danger?
This depends on the depth of the lesion – deep lesions are best left to the surgeon – as well as the topography. The ability to resist pain will depend on the size of the lesion. Any danger may arise from trying to lance an abscess that is close to a vital organ, such as an artery or large vein.

3. How can attach a compress without using adhesives?
There are dressings made with elastic net (Surgifix®) adapted to a limb, a part of a limb, or a depression, which keep a dressing in place without using adhesive plaster. This may be difficult in the folds of the groin, but the idea of using this kind of fixture is sound.

4. Can I benefit from help in the home when I am able to resume doing things about the house?
Yes; ask the social security services.

5. Should I take something to help me get through the nights, or to sleep better?
Yes, with the reservation that analgesics are not always very effective against pain caused by inflammation.

6. Are thermal cures advisable? And where?
There are no data.

7. How can I keep up physical activity if sport has become impossible?
Ask a physiotherapist or rehabilitation medic, but there are opportunities for using muscular contraction without movement, or movement of areas of the body not affected by the disease.. Remember, too, that walking is one of the best forms of physical activity there is, and no sufferer from HS should be kept for long in a state that prevents a brisk walk.

8. Can I swim in the sea or in swimming pools?
As far as the sea goes, yes. Regarding swimming pools, it obviously depends on the type of lesion you have. Using swimming pools should be avoided if you have oozing or suppurating lesions, out of consideration for other people.

26.7 Relations To Other Factors

1. Is articular (arthritic) pain related to the illness?
Articular pain can be related to the disease, but this is not true for all articular pains. It is known that some rheumatic inflammations may accompany diseases such as suppurating hidradenitis and that these joint symptoms may be

either peripheral (such as arms, legs, fingers) or in some cases central (such as pelvis or back).

2. Does tobacco provoke or aggravate the disease?
It has been demonstrated that HS is more prevalent among smokers than in the population as a whole, but it is not clear whether this is a cause or an effect, and it is not clear whether ceasing to smoke brings about an improvement – and indeed this cannot be proved either.

3. Is this a disease of the obese?
No, it is not a disease of the very fat. It also affects thin people, but being overweight is one of the factors that aggravates the disease and causes poor tolerance of the lesions.

4. Why should I not eat sugar, even if I am not diabetic?
There is no reason why you should not eat sugar.

5. Is a condition of extreme fatigue related to the disease?
It is difficult to interpret conditions of extreme fatigue. Permanent suppuration may lead to extreme fatigue, but extreme fatigue is also a symptom of depression, and HS can lead to a degree of depression.

6. Hair loss, brittle nails, dental abscesses, the loss of many teeth – are these related to the illness?
No, they have no relation to the disease.

7. Is there a risk of septic shock?
The risk exists in the form of an acute spread of the infection by means of a secondary streptococci infection, but this is extremely rare.

8. Are suppurations in the fold between the buttocks a form of HS?
An infection in the upper part of the fold between the buttocks is usually a pilonidal sinus, which is frequently associated with HS, but is different. The treatment is surgical and should be carried out by a surgeon very experienced in this type of intervention. HS lesions can be present in all of the perianal and perineal areas.

9. Why should I have a colonoscopy?
A colonoscopy may help to diagnose Crohn's disease, an inflammatory disease of the intestine, which can be accompanied by cutaneous symptoms, particularly perineal ones, and which can be confused with HS. However, faced with anal lesions not characteristic of HS or accompanied by digestive symptoms, a diagnosis of Crohn's disease simulating HS or associated with HS should be made, as there are specific treatments for Crohn's.

10. Can one develop the disease as the result of a blood transfusion?
No.

11. Can one give blood?
Yes.

12. Can frequent general anesthetics cause loss of memory?
No.

26.8 Psychological Aspects

1. Is stress a factor that may cause or aggravate the illness?
In many people stress may contribute to a worsening of the symptoms, but stress not a cause of the disease.

2. How do I break the news to my partner?
There is no recipe for this! This question and the next two require careful consideration.

3. How do I tell the family?
See Question 2 above.

4. Should I tell the family?
The same answer. But in any case you should make it clear that there is no risk to anyone else. It is also important to have someone with whom you can talk about the illness – relatives, friends or a doctor. It is essential to be able to give expression to the fact that you are ill in order to gain a little distance before considering the problems that the illness brings with it.

5. How should I tell my employer about the illness and the possibility that I may be absent from work?
The employer does not necessarily have to know the nature of the illness or the reasons for absence from work. However, if the disease affects your wok, perhaps raising a problem of your suitability for a job, the company doctor is the person to see.

6. What should I do if I get the blues?
See your GP, who can see if you are suffering from depression and if so recommend treatment, perhaps by a psychiatrist or a psychologist. It is never "normal" to feel depressed. You should not have to suffer the additional pain of depression because you have HS. An effective treatment of depression will not cure HS, but it will relieve you of some of the suffering that the illness may cause.

26.9 Children and Adolescents

1. What should I tell my child's teachers?
Your child may have trouble remaining seated for long periods, may need physical attention, and may be absent from school. This is a delicate problem, as it may be unacceptable to the child, especially if an adolescent, if all the teachers are aware of the health problem. The best solution may be to ask for a meeting with the school doctor or nurse. They can be informed in confidence about the problem, and they can provide teachers with information that may be necessary for practical reasons without divulging medical confidentiality.

2. What sports can a child pursue without risk of aggravating the disease?
In principle there is no reason why sports should aggravate the illness. But if the disease affects certain regions of the body, some sporting activities may become a source of difficulty (see below).

3. How do you talk about this illness with a young adolescent?
The important thing is to let the young person know that there is someone who is ready to talk with him or her. Let the adolescent talk, listen to his or her concerns, provide the information that he or she demands, without dramatizing too much, but without understating the situation too much either. Don't drown the child in information by trying to explain everything to a young person who does not want to listen or who is not ready for it. It is important to emphasize that the illness is not contagious, is not sexually transmissible, has no consequences for fertility, and the fact that some forms of the illness remain mild.

26.10 Social Security

1. Is the disease recognized as chronic?
It is not on the list of illnesses deemed "long and costly", but see Question 2.

2. Can the patient receive 100% cover by social security?
Yes, in certain cases and in some countries when a very detailed medical certificate is provided and a discussion is held with the relevant social security official and when the illness really is expensive.

3. Can the patient be recognized as disabled?
Yes.

Chapter 27

An Uncommon Valor

27

Sylvia Shawcross

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This chapter of this remarkable book does not take the form of a clinical paper: It is instead a collection of biographies given here specifically to impart to practitioners and health care professionals a glimpse into the world of their patients. It is, after all, the individuals with the disease hidradenitis suppurativa who are the reason why this book has been written. Their voices have long been silent. The advent of the internet as a means of communication has changed this silence into a chorus and perhaps now a deafening roar. I certainly hope so.

From 1996 to 2002 I had the privilege to work with and for fellow sufferers of the disease on the internet at a time when the 150-year silence was finally broken. At that time, we discovered caregivers were, for the most part, the only human beings that people with hidradenitis suppurativa would admit to having this disease in their "non-internet" lives. For some, even this was more than they could manage. I urge physicians not to take these last statements lightly. I urge you to think about this in light of the biographies that I am presenting to you here. Individuals who have this disease from my experience want knowledgeable and honest caregivers. In light of the lack of success with most treatments, compassion goes hand and hand with that care.

I could indeed write here about the issues this disease highlights. I could discuss antibiotic resistance, controversial treatment options, physician care that drives many to self-care, depression, suicide, lack of pain-management options, the physical problems of odor and leakage, lack of diagnosis or misdiagnosis, disability, healthcare costs, loss of self-esteem, disfigurement, secrecy, isolation, lost relationships, cultural taboos and nomenclature, confusion over and between treatment advisors, lack of treatment guidelines and the list goes on. Indeed I could discuss many things including a host of mythologies that have followed this disease for 150 years, but individuals with this disease can speak for themselves. Collectively they have that power now. They are finally free of their long, lonely and painful silence.

All that I have done and learned during those 6 years can be stated fairly succinctly: living with this disease creates a special human being, one infused with an uncommon valor in the face of overwhelming odds. Those odds are changing for the better. I believe that hope lies right now in your hands in the form of this book and the researchers, sufferers and the friends and families of sufferers who have made it their mission to change the situation for us all.

These biographies were collected from 1996 to 1997 and are from some of the first people who joined our internet support group. It was, at the

time, the only such support list available. The names of individuals have been changed otherwise the content remains as it was given.

27.1 Kevin

I have been searching the web for nearly a year now for HS information and every now and again I do another search in the hope I may find something "new". Today I was delighted to find your pages and especially the visitor's book with remarks from fellow sufferers which made me feel so much better about the way I feel.

I have been a chronic HS victim for a few years now and despite much sympathy from those in the medical profession – no ACTION. I visited a Naturapath nearly 2 months ago who put me on a "natural" diet and some homeopathic-type pills with ingredients you'd expect in a witches brew! The results so far have been very good and I can finally sleep uninterrupted and the swelling has nearly disappeared. So for the first time in years I am not in pain every second of the day... with the power of positive thinking I hope this will continue.

I'm a white male born 1962 in New Zealand (South Pacific Ocean). Fairly normal childhood in clean, green NZ. Mum, Dad and my 2 younger brothers went on a trip to California to visit an aunt in 1972. We sailed on the Canberra via Tonga, Hawaii and Vancouver. During this 6 month stay in USA I developed boils on my behind and thighs which were like volcanoes – very painful and not much fun for a 10 year old who had never really been sick before. One after another after another for months. It was thought I had contracted some tropical bug in Tonga. I don't know if it was HS then but no doctor we visited in California could diagnose what it was and tried different antibiotics, penicillin, etc. (I don't remember any exact details). Finally we went to see a specialist who prescribed something which worked almost immediately and the problem appeared to go away. I remember having these "boils" again maybe twice or three times during my teenage years. I had no acne problem as a teen, just normal zits. Later on, I would have been 22 or 23... I had what the doctor said was an abscess on my bum "probably from stress, bad diet or too much drinking or something" which healed with a course of antibiotics. This "thing" recurred from time to time for the next few years without any treatment. At the same time I got a pimple in my armpit which was never painful but seemed to fill up with a clear yellow fluid from time to time. I never really took much notice of it.

To be honest I wish I had, but I was too busy having a fun time. I spent from 23–29 travelling the world – I visited over 40 countries and it was a fantastic experience... When I arrived back in NZ in 1991 all hell broke loose. It was like someone or something had said "the party's over sunshine – your lifes gonna be like shit from now on!!"

My armpit swelled up like a tennis ball and my groin got worse and worse. Over the next couple of years it just spread to the point where I couldn't move without feeling like I had been stabbed with a hot knife.

Minocycline kept it in check – apart from the odd flare up – for about a year. Then last summer I was almost suicidal as it all erupted again. A double dose of Minocycline simmered this down but since then I knew it was just in a holding pattern and any minute it would spark up again and where would that leave me….

I don't know what has caused this terrible condition in me – we have no immediate family history of it or any other connections. I'm not really overweight either. One thing I have puzzled over is that when I was a teen and into my early 20's, I used to suffer from allergies (sneezing and runny nose, etc.) Then after I left NZ for those 7 years, these allergies pretty well went away – then I returned and this bloody thing erupted (could be something in the "air" my body rejects ??) but I don't suffer from hayfever or the sneezing fits from dust or pollen etc anymore – I can't help thinking this is somehow connected.

I wish my life was more normal. I wish I could play cricket again. I wish I didn't have to cover up all the time. I wish I could take my shirt off at the beach. I wish I could look forward to the future. I wish my son could climb on me.

27.2 Deborah

I don't mind sharing info. I'm 33. I have suffered with hidradenitis since I was about 10. Many doctors told me over the years that I had boils. These were very deep, open holes, leaving extensive scaring. They put me on many different medications, none of them worked so I went the surgery route. I have had 4 surgeries with my first in 1993. In '94 I had my arms and legs done. My legs alone required 80 stitches! My last surgery involved my groin area and they re-did my arms. Now I'm having problems on my back. I do not desire surgery again! I am frustrated and looking for suggestions and understanding. Your group is the first I've found and I'd like to belong!

27.3 Elizabeth

I'm 42 years old (43 next month) and have been getting lesions all my adult life. It's been much worse in the past 5 years – I always have 6–10 active abscesses. Areas affected – mostly in my groin and under my breasts. I hadn't had one in my armpits for years, but guess where I feel one starting now? (We all know "that old feeling", don't we?!) My dermatologist and I are presently trying different antibiotics – so far erythromycin and minocycline have failed to make the slightest difference. I'm now on cephalexin – so far there seems to be a very slight improvement – we'll see. I think there might be something to the theory that HS may be linked to the immune system – maybe our immune systems are attacking our sweat glands. This may be why one member sees such relief from prednisone. Most physicians think that HS is an infection, starting either in the eccrine and/or apocrine glands themselves or in the follicles. If it is strictly an infection, cortisone – an immune suppressant – would be contraindicated. Interesting.

My experience with physicians has been mostly positive – my internist and my dermatologist are very sympathetic. I saw my derm. on Monday. He doesn't "buy into the theory" that HS is autoimmune, he believes that it's a genetic defect that causes the apocrine glands to be prone to blockage and inflammation, and secondarily, infection. He also believes this genetic defect causes an androgen imbalance. He does, though, acknowledge that there are different theories about the cause. I've been on cephalexin for one month, with a slight improvement – since starting it I have an average of 6–8 abscesses continuously instead of the usual 8–10. He wants me to continue the antibiotic, and I will give it another month, but I don't want to take antibiotics long term unless the improvement is significant, which so far it isn't.

27.4 Melony

Hello!! I am 38 years old and I have had Hidradenitis Suppurativa since puberty. I get these cysts on my buttocks, inside of my thighs, and the groin area. I am very discouraged with this disease, as you probably know, there is no cure. That is what the doctors have told me. I have been on every kind of medication even Accutane. I have had surgery on my buttocks, have had some of the glands taken out, however, the cysts will come back as they cannot take every gland out of your body. I have had them lanced, which is really humiliating, because it just hurts so bad, but afterwards it is such a relief to have the cyst and the swelling gone. I have a cyst as we speak. I believe that stress causes these, and I tend to get them around that time of the month.

I really hate the way this disease has scarred me. Not only physically but emotionally. I am single, and I don't know who would want someone that has this. I'm really discouraged with this disease, I just cannot believe there is not a cure. I am very embarrassed with this, as my buttocks are really, really scarred, and the inside of my thighs are pretty bad also.

I am happy to find that there is support for this. I have never spoken to anyone that suffers from this. I sincerely know what they are going through. It really is comforting to know that I may be able to correspond with others that suffer from this.

I work at a college. I am a secretary, and I sit most of the time, which can be difficult at times.

I really try to do the best that I can do. I have resolved that I will have this forever and I will probably will be single the rest of my life. I am really scarred.

It seems that all the doctors that I went to were not sympathetic at all. I really don't think that humiliation and embarrassment begins to describe our feelings when we have to expose ourselves to doctors, etc. I remember, the last doctor that I seen, he was a plastic surgeon, and he really was the best doctor that I have seen. I really loved him. He was full of concern, and hated to see me in such pain. Unfortunately, he retired, and I try not to go to doctors unless it is absolutely necessary. I'll always remember going to his office. They always put me in this room that had a print of this little girl huddled in a corner, hiding her face, and there was this little dog sitting right next to her. The title of the print was "In Disgrace". How appropriate. I would cry as soon as I got in the room and seen the print. I could have been that little girl. I was in disgrace, but why. I searched and searched for a print of that, and finally found one. I truly related to that little girl. Every time, I went to his office, I left feeling disgraced.

This doctor performed a surgery on me. He went into detail about what he was going to do. He was going to go in and remove the glands, and he said that where he removed those, I shouldn't get anymore cysts. He explained that he couldn't take out all of the glands in my body, as we have millions of them. The surgery was on my buttocks. He did the surgery. I laid in the bed, on my back for four days. The nurses had to come and turn me over, as I couldn't move. On the fourth day the nurses came in, got me out of bed, had me lean across the bed, and proceeded to remove the bandages. I have never felt so much pain. Where I had lain so long, they had to use forceps to pull the bandages from the wounds. (Ouch, doesn't even touch it.) To add insult to injury, they put me in a tub of salt water afterwards. Just how much humiliation should one person have to go through??? I just don't know. I guess the surgery helped in some ways. However, my doctor told me to stay away from nudist camps (ha, ha).

27.5 Kerrie

My first outbreak, if you can call it that, showed up right before a vacation to Florida, which is why I remember it so clearly. I wore shorts at the beach as opposed to a bathing suit. It started then with one swollen red painful lump on the left side of my genital region. Since then, it's spread a bit. They are on both sides now – about 6 or more each side with little tunnels running between them. Around the time of my period one side or the other, rarely both, will become severely inflamed and horribly painful. I work twelve hours a day with a lot of walking, but ibuprofen seems to help some. I've only had a couple come to a head. When they're not inflamed, they range from pea sized to marble sized lumps under the skin. And some of them have what seem to be permanent holes in them that never close up. I went to my doctor about a year ago and he called them infected ingrown hairs and said they'd go away on their own. Sure. He put me on Tetracycline for my pimples I started getting after my son was born. That's why I think they are hormone related. Since his birth, the HS appeared, pimples appeared, I've had some excessive hair grown in the nether regions, and I have horribly painful and heavy periods that last up to two weeks every month. I'm going to see about birth control to help with that part of it. I've heard that can help HS too? I haven't needed birth control for years. I was divorced shortly after my son was born and since the HS appeared, I haven't even dated anyone. It seemed too embarrassing. Anyhow, I started surfing the net the other night looking up diseases and disorders of the skin, hoping I could find something that sounded like what I have. I came across a reference to HS and recognized myself immediately. I belong to an HMO and it's fun trying to see a doctor. Later today I plan to call my HMO and get a different doctor (the doctor I have now did a complete physical on me in less than five minutes. He was slamming patients in and out as fast as they could undress and dress), and then make an appointment for my official diagnosis. Since I spent a couple years in school learning med, I'm 99.993% sure that HS is what

I have. It's such a relief to have a name to put to my condition, and I'm pretty happy today, knowing what it is.

27.6 John

I've been having trouble with hidradenitis since my teens, I'm 44 now. Over the years it seems to flare up and give me trouble for extended periods and then subside, sometimes for a year or more with no trouble, except for mild acne mostly on my back.

For the first 10 years or so I didn't know what the problem was except that I would occasionally have to have a flare-up lanced. I just assumed they were boils and just the nature of my skin. Nobody (doctors) said anything. Then one time when I went to the doctor in need of lancing he referred me to a surgeon who referred me to a dermatologist. The dermatologist diagnosed my problem as hidradenitis. He prescribed Minocin in a low dosage, long term, along with cortisone injections into the infected sites. I feel the Minocin was a waste of money. I haven't had any success with any antibiotic in any form. The cortisone shots did help but would last only about 10 days and I could never get an appointment within the needed time frame so it would just flare up again and I would start all over.

My personal feeling is that the flare-ups are related to both stress and hygiene.

I seem to have some success by using Dial anti-bacterial soap both as a preventive and of course during flare-ups.

27.7 Caroline

I began to develop what I initially called "acne" and now know to be HS quite a number of years ago, probably when I was in my late 20s (I'll be 35 tomorrow). It began as very small cysts or pimples in my groin area or on my buttocks that initially would go away in a few days. I mentioned it briefly to a few doctors and was simply told I had ingrown hairs or folliculitis or it was from wearing jeans most of the time. Over the years, the frequency, size, and duration of them increased to the point where they became so painful and tender that all I could do after trying to sit all day at work, or even just walk, was to go home, sit in the bathtub, and cry, and sometimes just drink a lot to try to forget the pain. I again talked to my doctor, who responded in the usual fashion and told me I just needed to make sure to wash more often. The worst part was I couldn't even talk to anyone about it because it was so personal and embarrassing. If I had to take time off at work because I just couldn't sit any longer, I always had to come up with another excuse like having a migraine, etc.

Last week I had to see a dermatologist for another reason and happened to tell her about this problem. She knew right off what it was. I was so relieved to finally have a name for this problem. I was even half expecting for her to be able to just give me some antibiotics and it would go away, so, of course, I was shocked to hear that I would have to deal with this problem for the rest of my life. Although she was able to diagnose it, she wasn't very forthcoming about providing any information about the disease (other than it may be related to hormones) and I should consider taking estrogen. I was so dumbfounded by having a "lifetime" illness, and that I would have to deal with this pain, that I couldn't even think of questions to ask her. I went home and did some research and was really happy to come across this list and what it could mean for anyone that suffers from this illness.

At this point, I'm still at the angry and confused stage. This illness has not only affected my ability to work at times, but it also has (and is) affecting social and intimate relationships. But, I also know that half the battle is won now that I know what is it; I think the other half of the battle is being able to talk about it and get advice and support from others that suffer the same thing.

27.8 Arnold

I understand your concern for keeping the group "inclusive." Having suffered this disease for about 10 years now, it is a bit exciting – and a bit embarrassing – to share the experience with others.

First, just to let you know who is writing, I am a 58 year-old white male that has the disease in the groin, upper thigh and buttock areas. There is no known similar disease anywhere in the family that is known to me. I am within 10 pounds of my correct weight for height and age and have never had a weight problem. Marital status is currently single (my wife left me two years ago as a result of my various restrictions associated with the disease – not liking to be around "sick" people). So much for the "in sickness and in health" bit.

Over the years, I have been treated primarily with antibiotics (the whole gamut changing frequently) with little or no success. In November 1995 and February 1996, I underwent surgery to excise portions of my upper thighs and buttocks. Healing did not go well with about 20 inches of incisions taking the best part of a year to close and heal. These operations did nothing to slow down the spread of the disease.

In June 1996, I began a 20-week (80 milligram per day) treatment of Accutane which showed minor promise beginning about the 12th week with some of the more minor lesions healing (perhaps a 10–15% improvement?) and continued in that state until the course ended. My doctors – and I'm being treated at Johns Hopkins Hospital in Baltimore, Maryland – began a second round with the Accutane in June 1997 but at a much lower dosing of just 20 milligrams a day. To date, this has had no noticeable effect and the spread of the lesions is continuing. By the way, I suffered none of the side-effects associated with Accutane other than dry, chapped lips during the first course and nothing with this lighter than useless second course.

Pain is intense with every movement of my legs and while in the sitting position. After several months following the surgeries of controlling pain with narcotic pain relievers (Vicodin and Percocet), the doctors were unwilling to continue this treatment – more out of concern for themselves than with my pain, I might add. Through searching the Internet and talking with a chemist specializing in pain control substances, I stumbled upon Ultram. This is a wonderful non-narcotic pain reliever that is every bit as effective as Percocet but with a longer useful period, in fact, up to six hours. By the way, just to prove most recent studies done on pain medications, I had no trouble withdrawing from the narcotic type medicines nor did I display any addiction.

My doctors have been pushing me to undergo the radical surgery required of serious hidradenitis sufferers. I have insisted they continue to explore alternative potential remedies. Lo and behold, they have come to the conclusion that there is a very good possibility that I might be helped by low-level radiation treatments. Apparently, there is a disease that mainly affects Afro-Americans with very similar type lesions on the scalp and, I'm sorry, I've forgotten the name of that disease. Recent experiments with this low-level radiation have proven to be extremely helpful. My doctor has consulted with the chief of radiology at the hospital performing these experiments and they seem to think it could be helpful to me. I'm certainly willing.

27.9 Mabel

I live in South San Francisco, California and am a 40 year old female suffering from hidradenitis suppurativa since the onset of puberty. It has become progressively worse and in 1994 I had surgery to remove the abscesses from the groin area. I remained in the hospital for 3 months due to complications from the surgery (i.e. secondary infection). I had relief from the hidradenitis for only about 9 months after which time it returned to the areas under both arms. Since then I have been in constant pain and fatigue. I have been seeing a dermatologist who has me taking Eulexin, an androgen medication used for patients for prostate cancer. I also take the antibiotic dycloxicillin and vicodin for pain. The wounds seem to be responding to the Eulexin albeit ever so slowly. I've taking the Eulexin for a year come this November. The doctor has told me that I am only the second patient he has seen with such a severe case of hidradenitis. I can't tell you what a revelation it was to find a support group for those with this affliction! I truly thought I was the only one in the world with hidradenitis. And to cause even more frustration, no one had ever made the correct diag-

nosis during my early years. I wonder if they had diagnosed it early, if I might have gotten a "jump" on the disease and not become such a severe case. I did notice that during my two healthy pregnancies, this condition seemed to disappear for those wonderful nine months. As soon as the babies were born though, it reappeared and became progressively worse after each birth. This leads me to believe that it has a connection with some type of hormonal imbalance. It would be wonderful to have someone to "talk" to and who understands this terrible affliction.

27.10 Nassim

I really understand why you are asking for bios, I sometimes find it hard to share even with my family…I am 18 years old female from Turkey (so excuse me if my English is sometimes not good enough) I have had 3 surgeries until now, the first one 5 years ago from both of my armpits… And the others at anal zone. But I've been informed that I have this illness only 6 months ago… I've used a lot of antibiotics, only Tetradox was a little bit useful for me. I am using Roaccutane since 2 months right now, and I hope I won't have to have another surgery, cause it really doesn't work! :)

27.11 Mira

I do realize that this disease is a painful and very embarrassing one, as it has been that way for me also for many years. I am a 41 year old woman and have been suffering with this for 19 years. I first noticed this disease (although I didn't have any idea it was a chronic disease or that it had a name) when I was pregnant with my first child in 1977. I started getting what looked like "boils" that would come up and then go down on my buttocks. When one got big enough or painful enough to make me want to see a doctor, I was usually told it was a "boil" and that I should go home and put hot compresses on it until it came to a head, then come back to see him. Well they never came to a "head", but just eventually went back down.

In 1985, I was in the military and seen by a doctor there who said they were not "boils" but "cysts" and that I should let him "cut them out". Well I was afraid of the scarring and said "no". In 1987, those "boils" "cysts" abscessed and I had to have emergency surgery as they became one big gray mass on my right buttock and didn't look like it would go down by itself as usual. They found approx. 10 cystic like masses when they operated. The scar was very small and I didn't think much about it. I still didn't have a diagnosis except of "inclusion cysts on right buttock". About 4 months after the surgery, an infected "mass" came up over the surgery site and I was put on various strong antibiotics and told it was some kind of infection and it was "tracking". The mass would come up and burst open eventually and drain a lot of blood and pus. Finally one doctor sent me to the hospital as he felt I probably had more "cysts" down deep that needed to be cut out. Well, they did find what they described as about 15 cysts and a lot of "strange" tissue, so much so that they removed a lot of tissue from my right buttock (but I didn't know that until I went home and the bandage fell off prematurely). I didn't realize how much they had to cut, and assumed it would be similar to the first surgery, but I was wrong. They had to remove so much tissue that I have three scars going in all directions and about 1/3 of my tissue removed and my right buttock has a "caved in" look. I have lived with this many years and am very ashamed and embarrassed to let anyone (even another doctor) see it. At the beginning, nurses who saw it used to ask me if I have had radiation to the area.

Well, finally in 1995, I was sent to a doctor because more of these "cysts" "boils" were coming up around the surgery site, but not on the scar tissue of the surgery – and small ones on my face in front of my ears that were different from the ones on my buttocks as they didn't hurt and never went away. She diagnosed me with having hidradenitis and I finally had a name to put on it. The ones on my face seem to be spreading towards my nose as the years go on and I am very afraid of what my face will look like a few years down the road. I was seen by a plastic surgeon attached to a teaching hospital and he refused to operate on the ones in front of

my ears as he said that it would be dangerous to try to remove them as they wouldn't have a way to "drain" and might become a large inflammation with more scarring due to the surgery. I am also getting them on my left buttock now and am afraid that one day I will have to have surgery on that side which will then leave me with both buttocks very deformed looking.

I have recently gotten remarried and will not let my husband see or feel my buttock, as it is very embarrassing to me, although he says that it "doesn't matter to him." Well it does matter to me as the first time my ex-husband had seen the area after surgery in 1988, his face dropped. For the last 8 years of our marriage, I never again let him see it if I could help it. I feel like a woman who has had a mastectomy. Between having a very deformed right buttock with more lesions coming out around the surgical site and now having the lesions coming out on my left buttock, I feel like I am totally disgusting and unattractive. The ones on my face so far I have been able to cover with makeup, but I pray that they don't spread or get bigger.

27.12 Mindy

I have had Hidradenitis since I was 12 or 13. It kicked in not too long after I started menstruating. I saw my family doctor, who sent me to another doctor, who sent me to a dermatologist, who sent me to a gyno. Those 2 worked in conjunction with each other. My gyno had me on birth control pills my dermatologist had me on antibiotics, blood pressure medication, steroids, giving me cortisone shots right into the sore… I don't even know how many different medications I have been on.

About the time I was 18 and my mother could no long force me to go the doctor, I quit going. After at least 5–6 years of treatment, nothing was working…so I just decided to save all the money and quit throwing it away on pills and office visits. I have not received any further treatment since then and I am now 27. I have sores in the groin area, armpits and under my breasts. I also have a nasty little bugger right on my tailbone. That one comes and goes more than any of the others…at least once every 2 weeks that one will flare up and finally drain. Overall, I would say that the flare-ups are milder than they have ever been since I have been afflicted with this condition. Nonetheless, after years of flare-ups, I have so much scar tissue that the groin area looks like a war zone. Much of the skin in the area is purple and shiny from scarring. I have a constant open wound in the right armpit, but it doesn't seem to fill up…it just doesn't heal.

While this disease is very uncomfortable for me, physically and emotionally, I have always been thankful that it is a problem that no one knows about unless I tell them. All the marks and scars can be covered with clothes. There are a lot of diseases out there that cannot be hidden at all.

Editors note: Since this manuscript was completed a new patient organization has been launched with an international perspective. Further information can be found at: www.hs-foundation.org.

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