Importance Although the pathogenesis of hidradenitis suppurativa (HS) remains enigmatic, several factors point to potential involvement of the cutaneous microbiome. Insight into the cutaneous microbiome in HS using next-generation sequencing may provide novel data on the microbiological diversity of the skin.

Objective To investigate the follicular skin microbiome in patients with HS and in healthy controls.

Design, Setting, and Participants This case-control study obtained punch biopsy specimens from patients with HS (lesional and nonlesional) and healthy controls between October 1, 2014, and August 1, 2016. Data were analyzed from March to November 2016. Patients with HS were recruited from the Department of Dermatology, Zealand University Hospital, Roskilde, Denmark. Biopsy specimens were analyzed at the Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark. None of the participants received any antibiotics (systemic or topical therapy) within 1 month before the study. In patients with HS, biopsy specimens were obtained from lesional skin (axilla or groin) and nonlesional skin. Only nodules containing at least 1 visible hair follicle were biopsied. Biopsy specimens from healthy controls were obtained from the axilla only.

Main Outcomes and Measures The different microbiomes were investigated using next-generation sequencing targeting 16S and 18S ribosomal RNA.

Results The skin microbiome was characterized in 30 patients with HS (mean [SD] age, 46.9 [14.0] years; 19 [63% female]) and 24 healthy controls (mean [SD] age, 32.2 [12.0] years; 13 [54% female]). The next-generation sequencing data provided a previously unreported (to our knowledge) characterization of the skin microbiome in HS. The study demonstrated that the microbiome in HS differs significantly from that in healthy controls in lesional and nonlesional skin. Overall, the following 5 microbiome types were identified: Corynebacterium species (type I), Acinetobacter and Moraxella species (type II), Staphylococcus epidermidis (type III), Porphyromonas and Peptoniphilus species (type IV), and Propionibacterium acnes (type V). In lesional skin, microbiome types consisted predominantly of type I or type IV. Microbiome type IV was not detected in healthy controls. Several taxa, including Propionibacterium, showed a significantly higher relative abundance in healthy controls vs HS skin, indicating that Propionibacterium may be part of the pathogenesis in HS.

Conclusions and Relevance The study findings suggest a link between a dysbiotic cutaneous microbiome and HS.
Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of the hair follicle defined by recurrent nodules, tunnels (sinus tracts), and scarring involving the intertriginous regions. The nodules may progressively expand to abscesses and subsequently rupture, causing suppuration and malodorous discharge. The prevalence of HS has been estimated to be among 1% to 4% of the European populations.

Although evidence implies that aberrant immune responses have a role involving the innate and adaptive immune systems, the clinical picture of HS lesions appears reminiscent of bacterial infection. However, the structure of the bacterial population, as well as the diversity at the strain level, is poorly investigated in patients with HS. Previous studies have been restricted to lesional skin, without inclusion of healthy control groups. Most previous bacteriological studies in HS have primarily relied on culture-based methods, and the results often suggested that commensal bacteria (eg, coagulase-negative staphylococci) have a role in HS.

The emergence of next-generation sequencing (NGS) has allowed a more accurate and less biased characterization of microbiomes compared with culture-based techniques. Therefore, it appears attractive to investigate the microbiome of HS using NGS, thereby yielding a wider spectrum of species. We designed a case-control study investigating the skin microbiome using NGS targeting 16S and 18S ribosomal RNA (rRNA). Regions within the 6SrRNA gene give information on species-specific signature sequences, thereby providing valuable data for bacteria (16S) and for the identification of other organisms (18S) (eg, fungi). Insight into the cutaneous microbiome in HS using NGS may provide novel data on the microbiological diversity of the skin.

Methods

Ethical Statement and Study Design

This study was approved by the Ethics Committee of Region Zealand (project SJ-420) and the data protection agency (REG-105-2014) in Denmark. The study was conducted at the Department of Dermatology, Zealand University Hospital, Roskilde, Denmark, from October 1, 2014, to August 1, 2016. Data were analyzed from March to November 2016. Written informed consent was obtained from all study participants. An exploratory case-control study was designed to compare individuals with the diagnosis of HS (n = 30) with healthy controls (n = 24).

Study Participants

Participants with HS were randomly selected by consecutive recruitment of eligible patients from the Department of Dermatology, Zealand University Hospital. Healthy controls were recruited from the University of Copenhagen and from the health care staff at Zealand University Hospital.

Inclusion Criteria

All cases had a verified diagnosis of HS (International Statistical Classification of Diseases, 10th Revision, code L73.2) at the Department of Dermatology, Zealand University Hospital. An experienced dermatologist (D.M.S.) diagnosed all included patients. To verify the diagnosis of HS, histological biopsy specimens from lesional skin were obtained from all included patients. Furthermore, all patients were 18 years or older, were not pregnant, and experienced a flare of at least 1 painful nodule located in the axilla or in the groin.

Exclusion Criteria

Exclusion criteria were treatment with any antibiotics (systemic or topical therapy) within 1 month before the study (patients and healthy controls). Healthy controls were also excluded if any lesions compatible with HS were found. Moreover, all patients were 18 years or older, were not pregnant, and experienced a flare of at least 1 painful nodule located in the axilla or in the groin.

Skin Biopsies

Before injection of anesthetics, the skin was cleansed with ethanol (70% isopropyl alcohol) swabs. The HS lesional and nonlesional skin was anesthetized using a solution of lidocaine hydrochloride (20 mg/mL), and adrenalin (5 μg/mL), with no preservatives. In patients with HS, one 4-mm punch biopsy specimen was obtained from lesional skin (axilla or groin) and nonlesional skin. Biopsy specimens from HS nonlesional skin were obtained approximately 5 cm from the inflamed nodule and were clinically unaffected. Only nodules containing at least 1 visible hair follicle were biopsied in all participants. Biopsy specimens from healthy controls were obtained from the axilla only.

Microbiome Sequencing and Analysis

Biopsy specimens were analyzed at the Department of Microbiology and Infection Control, Statens Serum Institut, Copenhagen, Denmark. DNA was extracted using a kit (QiAamp DNA Mini Kit; Qiagen) according to the manufacturer’s instructions for tissues. For each batch of DNA extraction, a “negative” control was included containing buffers but no sample material for downstream analysis. DNA was amplified using a 2-step Polymerase chain reaction using custom 341F/806R primers targeting the V3-V4 16S regions, as well as 3 primer sets targeting the hypervariable regions V3-V4 of the 18SrDNA gene, and amplicons were sequenced on a desktop sequencer (MiSeq; Illumina, Inc) using the v2 reagent kit. For details concerning
primer design and library preparation, see the eAppendix in the Supplement. Sequence data are available at the European Nucleotide Archive (accession number PRJEB15266).

Statistical Analysis
All data analysis was conducted using a statistical software package (R, version 3.2.3; The R Project for Statistical Computing). Microbiome data were handled using the add-on package “phyloseq” version 1.16.2 and visualized with “ggplot2” version 2.1.0. Microbiome types were defined using vegdist (from the add-on package “vegan” version 2.3-2) and hierarchical clustering with default settings, and the number of optimal groups was decided by manual inspection.

Differences between groups were assessed with bar plots and principal coordinates analysis plots and tested with Kruskal-Wallis test or permutation test. Differential abundances (DAs) were tested using linear models, adjusted for anatomical location (axilla vs groin). Statistical analyses were performed for associations between the 5 microbiome types (Corynebacterium species [type I], Acinetobacter and Moraxella species [type II], Staphylococcus epidermidis [type III], Porphyromonas and Peptoniphilus species [type IV], and Propionibacterium [type V]) in the 3 groups (HS lesional skin, HS nonlesional skin, and healthy controls) and the variables sex, age, body mass index (BMI), smoking status, Sartorius score, and Hurley stage using Fisher exact test for categorical variables and Kruskal-Wallis test for continuous variables. A full statistical description is available in the eAppendix in the Supplement.

Results
The cutaneous microbiome was characterized in 30 patients with HS and in 24 healthy controls. In total, 83 punch biopsy specimens (30 HS lesional skin, 29 HS nonlesional skin, and 24 healthy controls) were obtained from patients with HS and healthy controls. Background factors and characteristics listed in the Table show that most of the participants with HS were predominantly female, younger, and smokers. Overall, our data demonstrated that the microbiome in inflamed HS nodules, nonlesional skin, and samples from healthy controls differed significantly from each other (Figure 1, Figure 2, and the eTable in the Supplement). The bar plot in Figure 1 shows differences in the bacterial community, with the 10 most abundant species or genera across the 3 groups. Several different unique types (I-V) of the skin microbiome were defined using hierarchical clustering of Bray-Curtis distances (Figure 1), a common dissimilarity metric used in ecology. Microbiome types in lesional skin consisted predominantly of Corynebacterium species (type I) and Porphyromonas and Peptoniphilus species (type IV). In contrast, Acinetobacter and Moraxella species (type II) dominated nonlesional skin. In healthy controls, the various microbiome types (I, II, III, and V) were more equally distributed. Microbiome types I and II were dominated by S epidermidis and P. acnes, respectively. Microbiome type IV was not detected in healthy controls, and microbiome type V was not found in HS lesional or nonlesional skin. The principal coordinates analysis plots (Figure 2 and eFigure 1 in the Supplement) show the significant differences between the 3 groups (overall F = 3.67 [between-group variance vs within-group variance, values above 1 indicate separation], P < .001; lesional vs nonlesional, F = 3.11, P < .001; nonlesional vs healthy controls, F = 4.21, P < .001; nonlesional vs healthy controls F = 3.65, P < .001, by Adonis PERMANOVA test) with and without stratification for anatomical location. There was no significant association between the number of species and the duration of lesions or the diameter of lesions.

In the 3 groups, no difference in richness (number of species per sample) was found (HS lesional median [IQR] 72 [59-82], HS nonlesional 72 [63-80], healthy controls 68 [59-78], overall P = .66, HS lesional skin vs HS nonlesional skin P = .97, HS lesional skin vs healthy controls P = .46, and HS nonlesional skin vs healthy controls P = .41) (Figure 3A). However, as shown in Figure 3B, an increased Shannon Diversity Index (a combined measure of evenness and number of species) due to increased taxonomic evenness (evenness between species) was found in nonlesional skin (median [IQR] 3.21 [2.84-3.91]) compared with lesional skin (2.80 [2.14-3.09], P = .02) and healthy controls (2.52 [1.88-2.95], P = .003) (overall P = .005), while lesional skin and healthy controls were not significantly different (P = .22). No interactions were found between the sample groups and anatomical location (linear models with vs without interaction terms; richness P = .54, Shannon Index P = .91).

The DA analyses at the genus and species levels yielded various differences between groups (Figure 4). At the genus level, the DA analysis showed a significantly increased relative abundance of Porphyromonas and Peptoniphilus species

Table. Background Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With HS</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total analyzed</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>19 (63)</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>46.9 (14.0)</td>
<td>32.2 (12.0)</td>
</tr>
<tr>
<td>White race/ethnicity, No. (%)</td>
<td>30 (100)</td>
<td>23 (96)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30.5 (7.7)</td>
<td>26.5 (2.6)</td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td>20 (67)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Sartorius score, mean (SD)</td>
<td>24 (10)</td>
<td>NA</td>
</tr>
<tr>
<td>Hurley stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 2</td>
<td>26 (87)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 3</td>
<td>4 (13)</td>
<td>NA</td>
</tr>
<tr>
<td>Location of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groin (n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axilla (n = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of lesions, mean (SD), cm</td>
<td>2.76 (1.38)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HS, hidradenitis suppurativa; IQR, interquartile range; NA, not applicable.

a P < .05 by Wilcoxon rank sum test.
b P < .05 by χ2 test.
Furthermore, Propionibacterium species showed a significantly higher relative abundance in healthy controls vs lesional skin (Figure 4A). At the species level, a significantly higher relative abundance of Pacnes and Corynebacterium striatum was found in the healthy control group compared with that in HS lesional skin (Figure 4B). This finding is also in congruence with the bar plot (Figure 1) showing microbiome type V (P acnes) as unique for healthy controls.

Shown are differences between the 3 groups (HS lesional skin, HS nonlesional skin, and healthy controls) in axillary and groin samples. Each lesional sample is connected with its corresponding nonlesional sample. Gray dots indicate samples from the opposite anatomical location (axilla or groin). Ellipses indicate the 75% prediction areas of samples from each group. HS indicates hidradenitis suppurativa.

(abundant in microbiome type IV) in lesional skin samples vs healthy control samples (Figure 4A). Furthermore, Propionibacterium species showed a significantly higher relative abundance in healthy controls vs lesional skin (Figure 4A). At the species level, a significantly higher relative abundance of
patients were more likely to have microbiome type II (72% [n = 13] vs males 45% [n = 5]). There was no difference in the distribution of axillary and groin biopsy specimens between the sexes (females 42% [n = 8] axilla samples vs males 64% [n = 7], \(P = .45\)). In patients with HS, no significant association was found between microbiome types and some variables, including age, BMI, smoking status, Sartorius score, and diameter of lesions. However, when correlating medication use (resorcinol monoacetate or azelaic acid) with the various microbiome types, medication was found to be associated with type I (treated 50% [n = 5] vs nontreated 5% [n = 1], \(P = .01\)) in nonlesional samples. In healthy controls, no significant association was found between sex, age, BMI, smoking status, and microbiome types.

Examining the correlation between beta diversity and these factors in lesional samples, we found a difference between biopsy locations (\(F = 2.05, P = .01\)), but not due to BMI (\(F = .49, P = .99\)), topical treatment (\(F = 1.07, P = .31\)), or smoking status (\(F = 0.85, P = .64\)) (eFigure 2A, eFigure 2B, and eFigure 3C in the Supplement). Stratified analyses showed that differences observed between groups were not confounded but remained significant despite stratification for these covariates (BMI<30 F = 2.05, \(P = .01\); axilla only F = 2.20, \(P < .001\); no treatment F = 3.25, \(P < .001\)) (eFigure 3A, eFigure 3B, and eFigure 3C in the Supplement).

The 18S analysis was also performed in Malassezia species. The analysis yielded no significant differences between groups.

Discussion

Overall, our NGS approach provided a previously unreported (to our knowledge) characterization of the skin microbiome in HS. The data demonstrated that the microbiome in HS differs significantly from that in healthy controls in HS lesional and nonlesional skin (Figures 1 and 2). This difference remained significant when stratifying for anatomical location of the samples (Figure 2). In addition, the DA analyses (Figure 4) showed significant differences at the genus and species levels between groups. Surprisingly, there were no differences in richness, the overall number of species found in each group (Figure 3A). However, in nonlesional skin, a significantly increased Shannon Diversity Index, which we interpret as increased taxonomic evenness, was found in axillary and groin samples (Figure 3B), indicating a possible imbalance (dysbiosis) of the microbial community in clinically normal-appearing HS skin.

The presence of anaerobic bacteria, such as Porphyromonas and Peptoniphilus species (type IV), has previously been reported in HS.\(^8,14\) Both bacteria belong to the spectrum of commensal bacteria on mucocutaneous surfaces.\(^16,17\) Guet-Revilleit et al\(^16\) recently investigated the microbiological profiles of 102 HS lesions using matrix-assisted laser desorption–time-of-flight mass spectrometry. In mature lesions, the study identified these types of bacteria (Porphyromonas and Peptoniphilus species) in 10 and 15...
Figure 4. Differential Abundance Analyses

A. HS lesional vs healthy controls at the genus level

B. HS lesional skin vs healthy controls at the species level

C. HS lesional skin vs HS nonlesional skin at the genus level

D. HS lesional skin vs HS nonlesional skin at the species level

Note significantly higher relative abundance of Propionibacterium in healthy controls and significantly higher relative abundance of Porphyromonas and Peptoniphilus. Note higher relative abundance of Propionibacterium in healthy controls than in lesional samples. C. Differential abundance at genus level between HS lesional skin and HS nonlesional skin. Note significantly higher relative abundance of Porphyromonas and Peptoniphilus in lesional skin than in nonlesional skin. Propionibacterium is more abundant in nonlesional skin. D. Differential abundance at species level between HS lesional skin and HS nonlesional skin. Note significantly reduced relative abundance of Propionibacterium acnes in HS lesional skin; higher relative abundances of Porphyromonas and Peptoniphilus are found in lesional skin. P values listed are adjusted for anatomical location. Black dots indicate the medians of each distribution.
Follicular Skin Microbiome in Hidradenitis Suppurativa and Healthy Controls

Kamp et al29 showed that sebaceous gland number and volume in HS. Although we did not find a reduced presence of microbiota in inverse areas,25 this finding lends credence to a hypothesis of an imbalanced skin microbiome preceding the development of HS lesions. This hypothesis may also be further supported by a 2012 study24 demonstrating alterations in leukocyte subsets (low-grade leukocytic infiltration) and histomorphology (follicular plugging) in normal-appearing HS perilesional skin. However, whether this subclinical inflammation and histomorphological changes occur before the development of the potential dysbiosis can only be speculated.

Our group recently demonstrated a significantly reduced presence of microbiota in preclinical HS skin compared with that in healthy controls using peptide nucleic acid–fluorescence in situ hybridization (PNA-FISH).32 The healthy controls showed a significantly higher presence of bacterial aggregates (biofilms) of a cocci morphology. All the HS biopsy specimens in the PNA-FISH study appeared as clinically normal-appearing skin with visible hair follicles. Most important, however, all the patients with HS reported a history of intermittent disease activity at the investigated site. With regard to the present NGS study, we did not obtain information on previous disease activity in the nonlesional area, and not all nonlesional biopsy specimens contained visible hair follicles. Therefore, the nonlesional skin in this NGS study and the preclinical skin in the PNA-FISH study may not be biologically comparable. Furthermore, NGS yields relative abundances, not absolute abundances, meaning that the data cannot be compared directly with a quantitative measure of biomass, such as PNA-FISH. However, HS is considered a chronic and systemic disease, with an unpredictable location of the lesions within the predilection regions. Therefore, the presence of bacteria consistent with a cocci morphology found in healthy controls (microbiome type III), but not in HS nonlesional skin, seems in agreement with the PNA-FISH findings.

Strengths and Limitations
The present study has several strengths. To our knowledge, no previous case-control studies have been conducted on the microbiological profiles of HS using NGS. Moreover, because HS is linked to pathogenic events of intertriginous hair follicles33,34 and due to the fact that bacteria are present in subepidermal compartments,35 we obtained biopsy specimens containing visible hair follicles only. In addition, biopsy samples were taken only from inflamed nodules, which potentially provides information on the early pathogenesis of HS. Last, no included participants received any antibiotics (systemic or local) within 1 month before the time of investigation.

However, potential limitations may also have influenced our results. Overall, microbiomes may vary by community, potentially limiting the generalizability. The few participants may have affected the statistical analysis and limited the generalizability to the larger HS population. We did not investigate chronic suppurating lesions. Furthermore, local isolates, respectively. Both bacteria have previously been found in the vaginal flora.19,20 This result is in congruence with our findings of an association of microbiome type IV and the groin, where secondary colonization from the vaginal flora or intimate contact with other partners may hypothetically occur. Alternatively, in particular, Porphyromonas species may have reached the groin indirectly from the oral cavity.21 Nevertheless, both bacteria have been described in chronic wounds and skin abscesses22,23 and may contribute to the chronicity and prolonged inflammation in HS lesions. Although we identified these species in inflamed HS nodules only, and not in chronic suppurating lesions, these species may have a role in the pathogenesis of HS at a much earlier event than previously considered. However, considering the intrapersonal variations of the skin microbiome between different skin sites, a comparison with the healthy controls may be somewhat biased because we did not obtain biopsy specimens from the groin among healthy controls. This absence may potentially have contributed to the lack of microbiome type IV in healthy controls. However, we found that the largest source of variation, even within individuals, was indeed the sample groups, as shown in Figure 2. Therefore, the potential dysbiosis in HS skin seems to outweigh any effects of the normal biogeographic diversity in the skin.

Although microbiome type IV was primarily associated with HS groin samples, Porphyromonas and Peptoniphilus species are indeed not considered part of the normal cutaneous microbiota in the human groin. Most important, the normal human axillary and groin microbiota are predominantly composed of Corynebacterium species, Propionibacterium species, and staphylococci species.24-26

Although P acnes has a well-described pathogenic role in acne vulgaris,27 it also serves as an abundant skin commensal that offers bactericidal properties against several other pathogens.25,28 In the perspective of the potential beneficial role of P acnes, the significant reduced relative abundance of P acnes in HS lesional skin compared with healthy controls may give rise to speculations on its clinical relevance. The potential underlying mechanism of this observation may reflect the pathogenic role of sebaceous glands in HS. Although we did not find a reduced presence of Malassezia species in patients with HS, using stereology, Kamp et al28 showed that sebaceous gland number and volume in patients with HS were significantly reduced compared with healthy persons. Furthermore, sebum excretion has also previously been shown to be reduced in HS.30 Most important, sebaceous glands are anoxic, and the secretion of sebum supports the proliferation of facultative anaerobic bacteria, such as P acnes.25 Therefore, the association between the reduction in number or volume in sebaceous glands and the subsequent alterations in the normal skin microbiota (eg, reduced presence of P acnes) may be part of the pathogenesis of HS.

In nonlesional skin from patients with HS, we found a significantly increased diversity of the microbiota compared with HS lesional skin and healthy controls, while the overall number of species was the same, indicating that HS nonlesional skin is characterized by a higher taxonomic evenness of several species. Although this result may reflect only the normal biological homogeneous distribution of the microbiota in inverse areas,25 this finding lends credence to a hypothesis of an imbalanced skin microbiome preceding the development of HS lesions. This hypothesis may also be further supported by a 2012 study24 demonstrating alterations in leukocyte subsets (low-grade leukocytic infiltration) and histomorphology (follicular plugging) in normal-appearing HS perilesional skin. However, whether this subclinical inflammation and histomorphological changes occur before the development of the potential dysbiosis can only be speculated.
keratolytic agents may have affected the follicular skin microbiome in 9 patients (eTable in the Supplement). Although we used ethanol swabs before performing biopsies, we did not obtain information on personal hygiene, which may affect the microbial community. In addition, we did not investigate the microbiome over time; therefore, our data represent points in a timeline, which may display fluctuations.

Conclusions

The observation that the microbiome in HS lesional and nonlesional skin differs significantly from that in healthy controls supports the hypothesis of a link between a dysbiotic cutaneous microbiome and HS. More studies are warranted to definitively assign a causative role for the cutaneous microbiome in HS.

ARTICLE INFORMATION

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Author Contributions: Dr Ring had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ring, Saunte, Miller, Fuursted, Jemec. Acquisition, analysis, or interpretation of data: Ring, Thorsen, Lilje, Bay, Theut Riis, Larsen, Andersen, Nielsen, Miller, Bjarnsholt, Fuursted, Jemec. Drafting of the manuscript: Ring, Lilje, Nielsen. Critical revision of the manuscript for important intellectual content: Thorsen, Saunte, Lilje, Bay, Theut Riis, Larsen, Andersen, Nielsen, Miller, Bjarnsholt, Fuursted, Jemec. Statistical analysis: Thorsen, Lilje, Theut Riis. Obtained funding: Bjarnsholt, Jemec. Administrative, technical, or material support: Ring, Saunte, Bay, Theut Riis, Andersen, Nielsen, Bjarnsholt, Fuursted, Jemec. Study supervision: Ring, Nielsen, Miller, Bjarnsholt, Jemec.

Conflict of Interest Disclosures: Dr Saunte reported being paid as a consultant for an advisory board meeting by AbbVie Denmark and reported receiving speaker’s honoraria or grants from the following companies: Bayer, AbbVie Denmark, Desitin, Pfizer, Galderma, Astellas, Novartis, and LEO Pharma. Dr Jemec reported receiving consulting fees from Abbott Laboratories, AstraZeneca, MSD, Novartis, Pfizer, and Dumex-Alpharma; lecture fees from Abbott Laboratories, Galderma, Pfizer, and Roche; grant support from Abbott Laboratories, Pfizer, Photocure, and LEO Pharma; equipment on loan from Michelson Diagnostics; and reimbursement for travel expenses from Abbott Laboratories, Galderma, and Photocure. No other disclosures were reported.

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Arsenic—ametalloidelement—hasanotablehistoryasatoxinandpois-son. TheGreekphysician Dioscorides first reported arsenic’s toxic potential in AD 40, particularly the gastrointestinal tract adverse effects associated with its ingestion.1 It is thought that 15 years later, Nero used arsenic to murder his stepbrother, Tiberius Britannicus, whose death facilitated Nero’s ascension as Emperor of Rome. Historically, arsenic has also been used as medical treatment for a variety of conditions, including several dermatologic diseases. With time, the cutaneous sequelae of arsenic exposure were increasingly appreciated, furthering the intrigue of a substance that over millennia has served as both poison and cure.

Hippocrates incorporated arsenic into corrosive salves and ointments for the treatment of ulcers and abscesses.2 Beginning in the 18th century, arsenic was increasingly used in Western medicine to treat a range of conditions. The English pharmacist and physician Thomas Fowler created an eponymous solution containing arsenic powder, potassium carbonate, and tincture of lavender. Fowler’s solution was administered as a tonic to treat leprosy, prurigo, and pemphigus, among other diseases.2–3 In the 19th century, arsenic was also a popular treatment for psoriasis with a narrow therapeutic range; it was often ineffective at low doses, and at high doses was associated with clinically significant ocular and gastrointestinal tract disturbances.2 During the early 20th century, arsenical compounds, such as arsphenamine and neoarsphenamine, achieved efficacy in treating syphilis,1 and were commonly used until the introduction of penicillin.

Arsenic’s widespread use in the 19th century led to observations of its significant adverse cutaneous effects. The French dermatologist Alphonse Devergie was among the first to describe hyperpigmentation resulting from extensive arsenic ingestion.1 In 1887, the English dermatologist Sir Jonathan Hutchinson proposed an association between arsenic exposure and development of keratotic and cancerous cutaneous lesions.3 Hutchinson described multiple patients treated with arsenic for several years for psoriasis who subsequently developed growths on the palms and soles, some of which ulcerated and others of which, on excision and microscopic examination, were revealed to be cancerous.3 Today, arsenical keratoses and arsenic-related nonmelanoma skin cancers are well-recognized lesions arising from chronic arsenic exposure. Systemic adverse effects associated with arsenic treatment included neuropathy, cirrhosis, and both hepatic and bladder cancers. These adverse effects and the introduction of safer, more efficacious treatments led to arsenic’s decline as a dermatologic treatment.

While arsenic is no longer used as therapy in dermatology, this unique substance continues to make a medical impact. Arsenic trioxide is a highly effective treatment for acute promyelocytic leukemia, and future medical uses for arsenic may be yet to be discovered.

**NOTABLE NOTES**

**Arsenic in Dermatology—From Dermatologic Therapy to Carcinogen**

Connie R. Shi, BS; Vinod E. Nambudiri, MD, MBA

Arsenic—a metalloid element—has a notable history as a toxin and poison. The Greek physician Dioscorides first reported arsenic’s toxic potential in AD 40, particularly the gastrointestinal tract adverse effects associated with its ingestion. It is thought that 15 years later, Nero used arsenic to murder his stepbrother, Tiberius Britannicus, whose death facilitated Nero’s ascension as Emperor of Rome. Historically, arsenic has also been used as medical treatment for a variety of conditions, including several dermatologic diseases. With time, the cutaneous sequelae of arsenic exposure were increasingly appreciated, furthering the intrigue of a substance that over millennia has served as both poison and cure.

Hippocrates incorporated arsenic into corrosive salves and ointments for the treatment of ulcers and abscesses. Beginning in the 18th century, arsenic was increasingly used in Western medicine to treat a range of conditions. The English pharmacist and physician Thomas Fowler created an eponymous solution containing arsenic powder, potassium carbonate, and tincture of lavender. Fowler’s solution was administered as a tonic to treat leprosy, prurigo, and pemphigus, among other diseases. In the 19th century, arsenic was also a popular treatment for psoriasis with a narrow therapeutic range; it was often ineffective at low doses, and at high doses was associated with clinically significant ocular and gastrointestinal tract disturbances. During the early 20th century, arsenical compounds, such as arsphenamine and neoarsphenamine, achieved efficacy in treating syphilis, and were commonly used until the introduction of penicillin.

Arsenic’s widespread use in the 19th century led to observations of its significant adverse cutaneous effects. The French dermatologist Alphonse Devergie was among the first to describe hyperpigmentation resulting from extensive arsenic ingestion. In 1887, the English dermatologist Sir Jonathan Hutchinson proposed an association between arsenic exposure and development of keratotic and cancerous cutaneous lesions. Hutchinson described multiple patients treated with arsenic for several years for psoriasis who subsequently developed growths on the palms and soles, some of which ulcerated and others of which, on excision and microscopic examination, were revealed to be cancerous. Today, arsenical keratoses and arsenic-related nonmelanoma skin cancers are well-recognized lesions arising from chronic arsenic exposure. Systemic adverse effects associated with arsenic treatment included neuropathy, cirrhosis, and both hepatic and bladder cancers. These adverse effects and the introduction of safer, more efficacious treatments led to arsenic’s decline as a dermatologic treatment.

While arsenic is no longer used as therapy in dermatology, this unique substance continues to make a medical impact. Arsenic trioxide is a highly effective treatment for acute promyelocytic leukemia, and future medical uses for arsenic may be yet to be discovered.

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