Pathophysiology of acne

Pathophysiologie der Akne

Klaus Degitz, Marianne Placzek, Claudia Borelli, Gerd Plewig
Department of Dermatology and Allergy, University of Munich, Germany

Section Editor
Prof. Dr. Michael Landthaler,
Regensburg

Introduction
Acne is the most common skin disease [1]. In Germany, as in other Western industrialized nations, a majority of the population has signs and symptoms of acne at least during puberty. Epidemiologic data suggests up to 80% of individuals are affected [2]. Men and women develop acne about equally. The disease has its onset at age 10–14 years and regresses by age 20–25 years. In some patients acne persists into the fourth or fifth decade of life (persistent acne). The clinical spectrum of acne ranges from mild manifestations (a few comedones with occasional inflamed papules or pustules, sometimes termed “physiologic” acne in contrast to “clinical” acne in more severe cases) up to severe inflammation and abscess formation on the face or upper trunk (Figure 1). Several classifications exist to describe the severity of acne [1, 3]. Independent of its severity, acne can be a heavy emotional burden on the patient.

Genetics
There is a genetic predisposition to acne and the concordance rate is high among identical twins. Little is known about specific hereditary mechanisms. Probably several genes are involved in the predisposition for acne [4]. These include the gene for cytochrome P-450-1A1 and for steroid 21-hydroxylase, which influences androgen production in the adrenal gland. People with a XXY karyotype often display a severe course of acne.

Pathogenetic factors and their clinical correlations
The current concept is that acne results from several interacting pathogenetic factors: seborrhea, follicular hyperkeratosis (comedones), microbial flora, inflammatory processes.

Seborrhea and follicular hyperkeratosis favor overgrowth of propionibacteria. Propionibacteria induce follicular and perifollicular inflammation especially due to chemotactic substances.

Epidemiologic data suggests up to 80% of individuals are affected.
The clinical spectrum of acne ranges from mild manifestations up to severe inflammation and abscess formation.

Probably several genes are involved in the predisposition for acne.
The current concept is that acne results from several interacting pathogenetic factors: seborrhea, follicular hyperkeratosis (comedones), microbial flora, inflammatory processes.
Inflammation is not only the result of the pathogenetic factors seborrhea, follicular hyperkeratosis and bacterial overgrowth. Recent experimental results show that initial perifollicular inflammation promotes follicular hyperkeratosis and thus the formation of comedones [5].

**Seborrhea**

With few exceptions (“free” sebaceous glands in the genital region and mucosa of the cheek), sebaceous glands are associated with hair follicles. Sebum is formed by dissolution of sebocytes in the sebaceous lobules (holocrine secretion), transported to the follicle by a draining sebaceous duct and reaches the skin surface via the infundibulum. The largest sebaceous glands are found on the face and upper trunk, i.e. regions where acne preferentially occurs. Large conglomerations of sebaceous glands associated with fine hairs are characteristic for sebaceous follicles.

It has been long known that sebum production in the sebocytes is regulated by androgens. Acne patients generally display increased sebum production (seborrhea). Eunuchs produce less sebum due to androgen deficiency and do not develop acne.

**Figure 1:** Patient with mild (a) and severe (b) acne.

**Figure 2:** Acne papulopustulosa.

**Figure 3:** Inflammatory lesion with rupture of the follicular wall. From [1].

The largest sebaceous glands are found on the face and upper trunk, i.e. regions where acne preferentially occurs.

It has been long known that sebum production in the sebocytes is regulated by androgens.
Androgens, sebum production and acne are closely associated at certain ages. In the first months of life temporarily increased androgen production leads to excess sebum and occasionally to acne of the newborn (acne neonatorum). After regression of early androgen production, little sebum is produced in childhood and acne is almost never observed. At an age of 8–10 years, the adrenal glands and later the gonads start producing androgens. This results in enlargement of the sebaceous glands, increased sebum production and acne in teenagers. The main sources of androgens are the adrenal glands and gonads, even though the skin itself is capable of synthesizing androgens. Androgens reach their target organs via the blood stream, affect gender differentiation, and promote musculoskeletal growth. In the skin they stimulate sebum production in sebocytes.

The main sources of androgens are the adrenal glands and gonads.

In most patients with seborrhea, increased sebum production occurs despite normal serum levels of androgens.

Seborrhea and acne are not only observed in the presence of normal blood levels of androgens, but also as a result of elevated androgen levels.

Frequent causes of hyperandrogenemia are polycystic ovarian syndrome and congenital adrenal hyperplasia. Seborrhea and acne can be caused not only by endogenous also by exogenously administered androgens

### Table 1: Plasma concentrations (nmol/l) and relative androgenic strength of androgens in adults. According to [15].

<table>
<thead>
<tr>
<th>Androgen</th>
<th>M</th>
<th>W</th>
<th>Relative androgenic strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydroepiandrosterone sulfate</td>
<td>1300–6800</td>
<td>1300–6800</td>
<td>1</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>3.0–5.0</td>
<td>3.5–7.0</td>
<td>2</td>
</tr>
<tr>
<td>Testosterone (1-2% free)</td>
<td>10–35</td>
<td>&lt; 3.5</td>
<td>20</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>0.87–2.6</td>
<td>0.17–1.0</td>
<td>60</td>
</tr>
</tbody>
</table>

Androgens, sebum production and acne are closely associated at certain ages. In the first months of life temporarily increased androgen production leads to excess sebum and occasionally to acne of the newborn (acne neonatorum). After regression of early androgen production, little sebum is produced in childhood and acne is almost never observed. At an age of 8–10 years, the adrenal glands and later the gonads start producing androgens. This results in enlargement of the sebaceous glands, increased sebum production and acne in teenagers. The main sources of androgens are the adrenal glands and gonads, even though the skin itself is capable of synthesizing androgens. Androgens reach their target organs via the blood stream, affect gender differentiation, and promote musculoskeletal growth. In the skin they stimulate sebum production in sebocytes.

The primary androgen regulating sebum production is dehydroepiandrosterone sulfate (DHEA-S). It is the androgen with the highest sebum concentration, being about equal in men and women (Table 1). DHEA-S is only a weak androgen, but sebocytes possess all necessary enzymes capable of intracellularly metabolizing DHEA-S into more potent androgens (Figure 4). After uptake in a cell, testosterone and dihydrotestosterone bind to a cytoplasmic androgen receptor, wander into the nucleus and bind there to specific gene sequences. Binding of the androgen-receptor complex affects the reading rate of the target genes. This results in an increased proliferation of sebaceous glands and increased sebum production; the responsible genes have not yet been identified. In sebocyte cultures, testosterone and dihydrotestosterone stimulate cell proliferation and lipid synthesis, to a higher degree in sebocytes from the face than in those from the legs [6].

In most patients with seborrhea, increased sebum production occurs despite normal serum levels of androgens. Increased sensitivity of sebocytes towards androgens is the presumed cause. Special importance is attributed to the enzyme 5α-reductase, which converts testosterone into the more potent dihydrotestosterone. Two isoenzymes of 5α-reductase with differing biochemical characteristics exist. Only isoenzyme 1 is strongly expressed in sebocytes and is thus potentially important for physiological sebum production, but also for the pathogenesis of acne. Cyproterone acetate, which is efficacious in treating acne, inhibits 5α-reductase. It is probable, nonetheless, that its effect is based on its antagonistic binding to the intracellular androgen receptor, as inhibition of type 1 5α-reductase alone does not improve acne [7]. Seborrhea and acne are not only observed in the presence of normal blood levels of androgens, but also as a result of elevated androgen levels. Elevated serum levels of androgen can occur in polycystic ovarian syndrome, androgen-producing tumors (e.g. adrenal adenomas, ovarian tumors such as hilar cell tumor) as well as congenital adrenal hyperplasia, which results from enzyme disturbances in the adrenal gland and is not quite so rare in its milder forms [8] (Table 2). Seborrhea and acne can be caused not only by endogenous but also by exogenously administered androgens. This might be iatrogenic during provocation of premature epiphysial closure to treat excessively tall stature or during substitution treatment of hypogonadism, but also due to androgenic anabolic
steroids (athletics, bodybuilding) [9]. Neuroendocrinologic effects on sebum production have been observed and may serve to explain psychogenic or stress-induced effects in the pathogenesis of acne. Among others, the neuropeptides corticotropin-releasing hormone and α-melanocortin induce sperm lipid synthesis in sebocytes in vitro. Acne patients possess an increased expression of the neuropeptide substance P and its degrading enzyme, neutral endopeptidase, around the sebaceous gland [10].

**Follicular hyperkeratosis**

A further prerequisite for developing acne is a disturbed follicular keratinization leading to hyperkeratosis. In normal hair follicles, keratinocytes are loosely layered. They are regularly desquamated and carried by sebum flow to the skin surface. There is a balance between newly produced and desquamated cells. In contrast, in follicles affected by acne there is an increased keratinocyte proliferation rate, the densely packed horny lamellae do not desquamate properly and are not transported by sebum to the skin surface (Figure 5). A retention-proliferation hyperkeratosis results, first as a non-visible microcomedo and finally as a comedo.

Several factors are held responsible for the follicular hyperkeratosis. These include changes in the lipid composition of sebum, bacterial metabolites and mediators of inflammation. One theory is based on the assumption that keratinocytes of the hair follicle are supplied with linolic acid via the sebum. Increased sebum flow in the face of a constant supply of linolic acid results in a decreased linolic acid concentration in sebum and thus a relative follicular deficiency in linolic acid. Overall linolic acid deficiency, such as in malnutrition, results in a generalized hyperkeratosis of exposed skin. In analogy, follicular hyperkeratosis in acne can be viewed as a localized, follicular linolic acid deficiency. Comedogenic sebum components serve as a further explanation. These include fatty acid peroxides and squalene peroxide, which is formed by UV-irradiation of the sebum lipid squalene. Comedogenic effects of androgens have been suspected, because antiandrogens reduced comedogenesis independent of sebum production in certain individuals. Recently, the body’s own inflammatory mediators have stirred scientific interest as possible comedogenic substance. It has been shown experimentally that the presence of a certain concentration of interleukin-1 is sufficient to produce follicular hyperkeratosis in a normal hair follicle [11].

**Microbial colonization**

*Propionibacterium acnes* is a pleomorphic diphtheroid rod and belongs to the resident flora of human skin. Propionibacteria are the dominant bacteria in hair follicles; they prefer microaerophilic or anaerobic conditions and preferentially colonize regions with high sebum production. Seborrhea and simultaneous follicular hyperkeratosis obviously promote proliferation of propionibacteria. A four log higher concentration of propionibacteria is found in 11- to 20-year-olds with acne in comparison to the similarly aged without acne. The role of propionibacteria in acne is due to strong proliferation with resulting increase in bacterial metabolites which have a proinflammatory effect.

**Figure 4:** Androgen metabolism of sebocytes (see text for further explanations).
action. Bacterial lipases were suspected at first, as they release fatty acids from esters. Free fatty acids above a certain concentration are irritative and proinflammatory. Later other potentially proinflammatory bacterial metabolites were identified such as proteases, hyaluronidases and chemotactic factors that can attract neutrophils and cause an inflammatory infiltrate in the follicular wall and in the surrounding dermis. When neutrophils enter a follicle and phagocytize propionibacteria, hydrolytic substances are released and further promote the inflammatory reaction. Propionibacteria are bound by the surface receptor TLR-2 (toll-like receptor 2). This binding induces monocytic cells, among others, to produce the inflammatory mediator interleukin-8, which chemotactically attracts neutrophils [12]. Propionibacteria activate the classical and alternative complement pathways. Besides these stimulating effects on the innate, unspecific immune system, interactions with the adaptive, antigen-specific immune system occur. Propionibacteria have a mitogenic effect on T lymphocytes.

Table 2: Causes of hyperandrogenemia.

<table>
<thead>
<tr>
<th>Adrenal cortex:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adrenogenital syndrome</td>
</tr>
<tr>
<td>• Adenomas</td>
</tr>
<tr>
<td>• Carcinomas</td>
</tr>
<tr>
<td>Ovaries:</td>
</tr>
<tr>
<td>• Polycystic ovaries</td>
</tr>
<tr>
<td>• Ovarian tumors (e.g. arrhenoblastoma, hilar cell adenoma, luteoma of pregnancy)</td>
</tr>
<tr>
<td>ACTH excess:</td>
</tr>
<tr>
<td>• Cushing syndrome (hypophysial and extra-hypophysial ACTH production)</td>
</tr>
<tr>
<td>XYY genotype</td>
</tr>
<tr>
<td>Exogenous androgen source:</td>
</tr>
<tr>
<td>• Testosterone injections</td>
</tr>
<tr>
<td>• Anabolic steroids</td>
</tr>
<tr>
<td>• Progestins with androgenic rest activity</td>
</tr>
</tbody>
</table>

Bacterial metabolites playing a role in acne: lipases, proteases, hyaluronidases, chemotactic factors.

Figure 5: Normal sebaceous follicle (left) and comedo (right). From [1].
Helper T lymphocytes reacting specifically to propionibacteria have been found in acne lesions. 
No conclusive experimental evidence exists for the pathogenetic relevance of colonization of sebaceous follicles by other organisms, especially coagulase-negative staphylococci or *Malassezia furfur*.

### Immunological factors and inflammation

Immunological and inflammatory factors influence the development and course of acne in various ways. For a long time, inflammation was viewed only as a result of the three other pathogenetic factors, especially bacterial metabolites. New data show that acne patients possess a tendency to follicular inflammation from the outset [5]. It is presumed that leukocytes by production of cytokines such as IL-1 and thus pave the way for acne development. Inflammatory processes can also increase sebum production. The inflammatory mediator leukotriene B4 binds to a receptor on sebocytes, peroxisome proliferator-activated receptor-α which regulates lipid metabolism. This relationship is supported by the observation that the leukotriene antagonist zileuton leads to decline in sebum lipids [13].

### Trigger factors

According to current understanding, the interaction of the pathogenetic factors is sufficient for acne to develop independent of outside factors. Trigger factors are known which are capable of worsening acne or cause it to appear. In women, premenstrual aggravation of clinical symptoms is well-known; the hormonal background is not exactly clear. One explanation is the premenstrual narrowing of the sebaceous follicle and irregularity in sebum secretion, possibly due to estrogen-induced increased hydration of the follicular epithelium [14]. Various drugs can aggravate acne or cause it to appear. Further, monomorphous acneiform eruptions with uniform erythematous papules can be observed. In these acneiform eruptions, damage to the follicular epithelium by the causative drug is postulated, even without seborrhea or follicular hyperkeratosis. Follicular contents empty into the perifollicular connective tissue with resulting inflammation. Frequently involved drugs are the systemic glucocorticoids; further substances are listed in Table 3. Recently, a new class of chemotherapeutic agents, the EGF-receptor antagonists, has been recognized as triggers of acneiform eruptions (gefitinib, erlotinib, cetuximab).

Acne venenata (contact acne or acne cosmetica) is a variant of acne induced by exogenous factors. Occurrence in atypical locations and outside of typical age groups points to the exogenous cause. Trigger factors include comedogenic ingredients (e.g. isopropyl myristate, cocoa butter, lanolin, butyl stearate, stearyl alcohol, oleic acid) or too greasy or oily foundations of skin care products. Often, patients do not recognize

<table>
<thead>
<tr>
<th>Table 3: Drugs triggering acne or acneiform eruptions (selection).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs triggering acne or acneiform eruptions (selection):</strong></td>
</tr>
<tr>
<td>• 8-methoxypsoralen + UVA</td>
</tr>
<tr>
<td>• Actinomycin D</td>
</tr>
<tr>
<td>• Androgens, anabolics</td>
</tr>
<tr>
<td>• Progestins mit androgenic rest activity (e.g. 19-nortestosterone derivatives)</td>
</tr>
<tr>
<td>• Disulfiram</td>
</tr>
<tr>
<td>• Glucocorticoids, ACTH</td>
</tr>
<tr>
<td>• Isoniazid</td>
</tr>
<tr>
<td>• Psychopharmacologic agents (phenytoin, chloral hydrate, lithium)</td>
</tr>
<tr>
<td>• Tetracyclines</td>
</tr>
<tr>
<td>• Vitamin B6 (pyridoxine), vitamin B12 (cyanocobalamin)</td>
</tr>
<tr>
<td>• EGF receptor antagonists in chemotherapy of solid tumors</td>
</tr>
</tbody>
</table>

For a long time, inflammation was viewed only as a result of the three other pathogenetic factors. New data show that acne patients possess a tendency to follicular inflammation from the outset [5]. Inflammatory processes can also promote acne by increasing sebum production.

Trigger factors for acne include: female menstrual cycle, drugs, chemical contactants, and mechanical irritation.

In acneiform eruptions, damage to the follicular epithelium by the causative drug is postulated, even without seborrhea or follicular hyperkeratosis.

**Acne venenata**
the association of skin care products with acne. Similar clinical features can result from contact with pomades or hair gels, as well from contact with tar fumes. Chloracne is a form of acne induced by halogenated aromatic compounds. Best known is dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin), that caused the environmental catastrophe in Seveso, Italy, in 1976. Dioxin can cause severe acne with abscess formation that is difficult to treat. Beyond provocation by chemical substances, physical irritation can trigger acne, for example by friction or chafing (acne mechanica) of a shirt collar. An iodine-rich diet of algae and vitamin B complex products as nutritional supplements can trigger a worsening or development of acne. Triggering of acne by food has long been held insignificant, but recently has gained attention. New epidemiological observations suggest that diet can play a role; populations with a natural lifestyle do not develop acne. Various hypotheses correlate acne with western diet (e.g. with dairy products and with the promotion of hyperglycemia, thus increasing production of insulin and other growth factors and thus producing seborrhea and follicular hyperkeratosis).

Summary
Various factors are of pathogenetic relevance in the development of acne, especially seborrhea, follicular hyperkeratosis, propionibacteria and inflammatory processes. Seborrhea and follicular hyperkeratosis together promote proliferation of *Propionibacterium acnes*, a member of resident flora. The increased metabolites and chemotactic factors released by propionibacteria lead to follicular inflammation and in extreme cases to marked perifollicular inflammation. Sebum production is hormonally regulated by androgens, and disturbances in androgen metabolism can trigger acne. Follicular hyperkeratosis can be caused by a relative linolic acid deficiency, the effects of fatty acids and squalene peroxides, and inflammatory mediators. Bacterial metabolites, such as lipases, hyaluronidases, proteases and chemotactic factors, have proinflammatory effects. Inflammation is, however, not only a result of seborrhea, follicular hyperkeratosis and excessive overgrowth of bacteria. A perifollicular inflammatory predisposition may exist from the onset, promoting follicular hyperkeratosis, comedogenesis and thus the initiation of acne. Trigger factors include, among others, fluctuations in the female menstrual cycle, certain drugs, comedogenic contactants (e.g. in cosmetics) and mechanical irritation. The role of diet in the development and course of acne has only recently attracted new attention, but still must be defined more clearly.

Correspondence to
Prof. Dr. K. Degitz,
Pasinger Bahnhofsplatz 1
D-81241 Munich, Germany
Tel: +49-89-88 88 48 0
Fax: +49-89-82 04 58 0
E-mail: Klaus.Degitz@lrz.uni-muenchen.de

References
8 Placzek M, Arnold B, Schmidt H, Gaube S, Keller E, Plewig G, Degitz K. Elevated 17-
hydroxyprogesterone serum values in male patients with acne. J Am Acad Dermatol
9 Degitz K, Placzek M, Arnold B, Plewig G. Endokrinologische Aspekte bei Akne. In:
Plewig G, Degitz K. (Hrsg): Fortschritte der praktischen Dermatologie und Venerolo-
10 Zouboulis CC, Böhm M. Neuroendocrine regulation of sebocytes – a pathogenetic
176–182.
D, Cunliffe WJ, Akira S, Sieling PA, Godowski PJ, Modlin RL. Activation of toll-like recep-
tor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002; 169:
1535–1541.
13 Zouboulis CC, Nestoris S, Adler YD, Orth M, Orfanoes CE, Picardo M, Camera E,
Cunliffe WJ. A new concept for acne therapy: a pilot study with zileuton, an oral 5-li-
14 Grabmeier B, Landthaler M, Hohenleutner S. Menstruationszyklus und Haut. JDDG
15 Orth DN, Kovacs WJ. The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg
HM, Larsen PR, (eds): Williams textbook of endocrinology. Philadelphia: W.B. Saun-