The Pathophysiology of Acne Vulgaris in Children and Adolescents, Part 1

Wilma F. Bergfeld, MD

GOAL

To understand the pathophysiology of acne vulgaris in children and adolescents

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the pathophysiology of acne.
2. Explain how adrenarche influences acne.
3. Discuss the role of androgens in the development of acne.

CME Test on page 112.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: July 2004.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only that hour of credit that he/she actually spent in the activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Dr. Bergfeld reports no conflict of interest. The author reports no discussion of off-label use. Dr. Fisher reports no conflict of interest.

Microcomedones, the earliest lesions of acne, appear at adrenarche, which typically occurs at about 8 years of age when androgens of adrenal origin begin to stimulate follicular hyperkeratosis and sebaceous hyperplasia in pilosebaceous units on the face. Comedones appear about 2 years later, when androgens of gonadal origin are produced and colonization of follicles by Propionibacterium acnes *increases. Inflammatory lesions, such as pustules, papules, and nodules, are the result of the host's immune responses to* P acnes; *the proinflammatory cytokines are released by immunocompetent leukocytes that are recruited in response to this bacterium and its metabolic by-products. Androgens also affect the barrier function of the skin, and disturbances of barrier function may stimulate epidermal DNA synthesis. This leads to epidermal hyperplasia, which may also contribute to follicular hyperkeratosis in acne. Optimal treatment for this disorder will address these various pathophysiologic factors.*

Cutis. 2004;74:92-97.

Accepted for publication June 14, 2004.

Dr. Bergfeld is Head, Dermatological Research, Department of Dermatology, Cleveland Clinic, Ohio, and Clinical Associate Professor, Department of Dermatology, Case Western University, Cleveland.

Reprints: Wilma F. Bergfeld, MD, Cleveland Clinic Foundation, 9500 Euclid Ave, A61, Cleveland, OH 44195 (e-mail: bergfew@cesmtp.ccf.org).

Acne is predominantly a disorder of late childhood and adolescence, despite the fact that it may persist into, recur, or begin during adulthood. Although acne has been reported in otherwise healthy children as young as 8 years,[1] and even earlier in those with abnormal virilization or precocious puberty,[2] most cases occur between the ages of 14 and 19 years.[1] The prevalence of acne was assessed among 6768 boys and girls aged 12 to 17 years in the National Health Examination Survey of 1966 to 1970.[3] Based on physical examinations, only an estimated 27.7% of children were found to have essentially normal skin, whereas 68.1% had lesions diagnosed as facial acne (minimal requirement for diagnosis was sparse comedones with no inflammatory reaction). Prevalence increased with age more rapidly among younger than older youths, from 39% at age 12 years to 86.4% at age 17 years, and the increase in prevalence with age was more rapid and consistent among boys than girls. Although facial acne was about as prevalent among girls as boys in the 12- to 17-year age range (69.8% and 66.4%, respectively), the onset occurred somewhat earlier in girls, and the severity tended to be greater in boys. More severe facial acne (defined in the survey as at least comedones, small pustules, and a tendency toward inflamed lesions deeper than the follicular orifice) was present in a much smaller proportion of youths.

More recently, estimates from the National Health Interview Survey of 1996, which included 24,371 households containing 63,402 persons, identified "chronic" acne (acne with a duration >3 months) in 2.44% of those 17 years and younger,[4] which corresponds approximately with the prevalence of "more severe facial acne" in the earlier survey. These results suggest a relationship between the onset of puberty and the pathophysiology of acne. This article reviews recent advances in our understanding of acne in children and adolescents, with an emphasis on the triggering role of adrenarche. Part 2 of this article will review treatment options.

Pathophysiology of Acne

A number of pathophysiologic factors contribute to the development of acne, beginning with increased prepubertal androgen production, followed in a generally sequential manner by abnormal pilosebaceous follicular keratinization and desquamation; increased proliferation of sebocytes, enlarged sebaceous glands, and augmented secretion of sebum; obstruction of sebaceous follicles; colonization of pilosebaceous units by *Propionibacterium acnes*; and perifollicular inflammation.[5-13] Follicular hyperkeratinization, sebocytic hyperplasia, and seborrhea are all dependent on androgens.[14-16]

Role of Adrenarche

The pathogenetic process appears to commence with androgenic hormonal stimulation of pilosebaceous units, the density of which is greatest on the face and scalp (400–800 glands/cm^2) and least on the extremities (50 glands/cm^2).[5] Before levels of circulating androgens increase, pilosebaceous units consist of soft, fine, unpigmented vellus hairs and small sebaceous glands.[17] Circulating androgens bind to androgen receptors that are localized to the basal layer of the outer-root–sheath keratinocytes of the hair follicle and to sebaceous glands.[15] In sexual hair areas, such as the axilla, pilosebaceous units begin to differentiate into large terminal hair follicles. In sebaceous areas, such as the face, pilosebaceous units become sebaceous follicles while the hair remains vellus.[17] Without a source of circulating androgens, the sebaceous glands remain small.[6]

The adrenals and the gonads produce the majority of circulating androgens.[15] During the prepubertal period, adrenal androgens appear to be the major determinant of sebaceous gland activity.[18] In both boys and girls, plasma concentrations of the adrenal androgens dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) normally begin to increase at adrenarche, or adrenal puberty, which typically occurs at about age 8 years, and continue to rise through puberty.[19] Conditions such as adrenal hyperplasia or polycystic ovary disease are associated with hyperandrogenism; sudden onset of acne or treatment-resistant acne may be associated with these conditions.[15]

Androgen stimulation drives the changes in both follicular keratinocytes and sebocytes that lead to the formation of microcomedones,[10] which are not visible but are already present in 40% of children aged 8 to 10 years.[17] Microcomedones develop when desquamated cornified cells of the upper canal of the sebaceous follicle become highly adherent and obstruct the lumen in the presence of increased sebum production (retention hyperkeratosis).

The onset of adrenal production of DHEA and DHEAS is followed by a rise in plasma levels of adrenal androstenedione 1 to 2 years later, which approximately coincides with an increase in gonadal testosterone production—the so-called gonadarche or pubarche. It is at this time that microcomedones begin to enlarge and become visible, forming open and closed comedones, which are noninflammatory lesions.[10] This comedogenesis

may be driven in part by increased levels of interleukin 1α, which is derived from ductal keratinocytes.[20] Colonization of the follicular canal with *P acnes*, an anaerobic, aerotolerant, lipophilic diphtheroid that thrives in triglyceride-rich sebum, follows comedogenesis.[21] Inflammatory acne appears to be the result of the host response to *P acnes* and the proinflammatory cytokines released by immunocompetent cells that are recruited by this bacterium and its metabolic by-products.[11,13,21,22] Depending on the intensity of the inflammatory process and its localization within the follicle, erythema, superficial pustules, papules, and/or nodules (cysts) may develop.[7] Most patients have a variety of noninflammatory and inflammatory lesions, though some have predominantly one type or the other.[8] It is currently believed that hypersensitivity to *P acnes* determines the magnitude of the immunologic response and, accordingly, the severity of inflammatory acne in individual patients.[23]

It has been proposed that peptidoglycan and lipoteichoic acid from the cell wall of *P acnes* can amplify the immune activity of androgen-stimulated keratinocytes and sebocytes. This occurs predominantly through toll-like receptors with an increased release of cytokines such as IL-1α, IL-8, and tumor necrosis factor α from these cells.[13] Abnormal lipids in sebum also may affect the immune activity of keratinocytes and sebocytes, thereby directly influencing their proliferation and differentiation and the release of various cytokines. These cytokines, in turn, can activate endothelial cells and immunocompetent cells, such as neutrophils and T lymphocytes, which then participate in the inflammatory process.

Pilosebaceous units are targets for circulating androgens; in addition, they can synthesize the relatively weak androgens DHEA and DHEAS de novo from cholesterol.[24] Pilosebaceous units also are able to convert DHEAS to androstenedione through the action of 3 β-hydroxysteroid dehydrogenase (3 β-HSD) and to convert androstenedione to the more potent androgen testosterone through the action of 17 β-HSD.[25] Testosterone, in turn, can be converted by the action of 5 α-reductase to dihydrotestosterone (DHT)—the most active androgen metabolite in the pilosebaceous unit[26]—with an affinity for the androgen receptor that is 5- to 10-fold greater than that of testosterone.[15] DHT is primarily responsible for androgen receptor binding and end-organ effects in the skin,[27] and excessive DHT formation in the skin has been implicated in the pathogenesis of acne, suggesting that activity of 5 α-reductase may be a contributory factor.[17] For example, Imperato-McGinley and colleagues[28] showed that patients with an inherited 5 α-reductase deficiency and decreased DHT produced no sebum, just as preadrenarchal children produce no sebum. In a 5-year longitudinal study of adolescent girls, Lucky and colleagues[29] observed a correlation between early onset of acne, androgen levels, and more severe comedonal acne later. Girls who experienced early onset of acne had higher levels of DHEAS, testosterone, and free testosterone. The researchers speculated that DHEAS appears to be involved in the initiation of acne.[29]

Concentrations of testosterone and DHT can be decreased by local conversion to estrogens; to weaker androgens such as 3 α-androstenediol; or to glucuronide conjugates such as 3 α-androstanediol glucuronide, which are more rapidly cleared from the circulation. Fritsch and coworkers[30] studied messenger RNA expression patterns of the androgen receptor and androgen-metabolizing enzymes in human skin cells and found that sebocytes are the key regulators of androgen homeostasis. These investigators observed that sebocytes were able to both synthesize testosterone from adrenal precursors and inactivate it to maintain local concentrations of androgen, whereas keratinocytes only inactivate androgen.[30]

Plasma Levels of Androgens Versus Androgen Sensitivity

The severity of facial acne increases with the degree of development of secondary sex characteristics among boys aged 12 to 16 years and girls aged 12 to 15 years, suggesting a relationship with circulating sex hormones.[3] Some patients with facial acne have increased levels of circulating androgens, and serum levels of DHEAS are significantly higher in prepubertal girls with both comedonal and inflammatory acne compared with those without acne.[15] In most cases, however, measurable variations in circulating androgens do not differentiate those persons with either mild or severe acne from those without acne.[7] Rather, the development of acne appears to depend primarily on end-organ sensitivity, or hyperresponsiveness, to normal levels of circulating androgens.[1] For example, the activity of 5 α-reductase and 17 β-HSD in skin varies in different regions of the body[15]; specifically, the activity of 5 α-reductase in sebaceous glands of facial skin is greater than that in sebaceous glands of skin that is not prone to acne. The enzyme 5 α-reductase catalyzes the conversion of testosterone to the more potent DHT, thereby suggesting a relationship between increased local concentrations of this potent androgen and facial

acne. In contrast, the oxidative activity of 17 β-HSD is greater in sebaceous glands of skin that is not prone to acne. The principal activity of this enzyme is to convert testosterone back to the less active androstenedione, suggesting that local concentrations of testosterone remain higher in facial skin than in skin that is not prone to acne.

Effect of Androgen on the Epidermal Barrier and Keratinocyte Proliferation/Differentiation

The stratum corneum is a rate-limiting semipermeable barrier to the passage of water, electrolytes, and other molecules between the external environment and internal milieu.[31] It is composed of keratinocytes and a lipid-rich intercellular matrix of sphingolipids, cholesterol, and free fatty acids.[32] Lipid synthesis occurs in all nucleated layers of the epidermis, and epidermal lamellar bodies then deliver the newly synthesized lipids to the interstices of the stratum corneum, leading to water barrier formation. In addition to androgen's effects on the pilosebaceous unit, androgens modulate epidermal growth and differentiation, including important influences on the intercellular matrix of the stratum corneum, which mediates both transcutaneous water loss and absorption and percutaneous absorption of foreign substances such as pharmaceuticals.[33]

Interestingly, the stratum corneum of a full-term human neonate possesses a normal barrier function, whereas the stratum corneum of a preterm neonate is thinner and has an insufficiently developed barrier function.[31] Androgens delay the development of this cutaneous permeability barrier in utero, while estrogens accelerate barrier development. A gender difference with respect to fetal development of barrier function also has been noted[34]; male murine fetuses have demonstrated slower barrier development compared with female littermates, an effect that was reversible with the prenatal administration of the androgen receptor antagonist flutamide. Flutamide exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting nuclear binding of androgens in target tissues.

Based on these observations in fetal skin, Kao and colleagues[35] evaluated the effects of testosterone on barrier homeostasis in adult murine and human skin. Hypogonadal (due to castration or systemic flutamide) male mice displayed significantly faster barrier recovery at 3, 6, and 12 hours following sequential cellophane tape stripping compared with controls; topical testosterone replacement slowed barrier recovery in castrated male mice. Topical, as well as systemic, flutamide accelerated barrier recovery in controls, indicating that testosterone directly affects the skin. The investigators also found that barrier recovery was slower in young adult male mice compared with prepubertal male mice. The researchers attributed this difference to the fact that serum testosterone levels are 60% to 70% lower in prepubertal male mice than in postpubertal male mice. The investigators also demonstrated repeated changes in barrier recovery that paralleled peaks and nadirs in serum testosterone levels during intermittent hormone replacement in a hypopituitary human subject. Finally, the investigators studied the ultrastructure of the skin of subject animals. Kao et al noted no difference in sebaceous lipid synthesis but did observe that the thickness of the stratum corneum decreased in testosterone-replete animals because of decreased lamellar body formation and secretion.[35]

The clinical implications of these findings are unclear because skin diseases that may be associated with compromised barrier homeostasis appear to be as common in women as men. However, gender may influence the severity rather than the prevalence of some dermatologic disorders, such as acne, through its impact on barrier function. For example, it has been postulated that follicular hyperkeratosis in acne may result from a linoleic acid deficiency in the follicular epithelium[36] and that retention of desquamated cornified cells in the follicular canal is caused by an imbalance of free sterol and cholesterol sulfate in comedonal lipids.[37] In addition, acute or chronic disturbances of barrier function may stimulate epidermal DNA synthesis, leading to epidermal hyperplasia, which also might contribute to follicular hyperkeratosis in acne.[32]

Yamamoto and coworkers[38] examined the role of the sebum secretion rate and the lipid content and barrier function of the stratum corneum in 36 patients with acne and 29 controls. The sebum secretion rate over 3 hours was significantly greater in patients with moderate acne, but not mild acne, compared with controls. Sphingolipids (ceramides and free sphingosine) in the stratum corneum were significantly different among patients with moderate acne, mild acne, and controls, with the lowest concentrations in patients with moderate acne. Similarly, barrier function was reduced to the greatest extent in patients with moderate acne, with lower levels of sphingolipids corresponding to diminished barrier function. These results suggest that an impaired barrier function caused by decreased amounts of ceramides may be responsible for the formation of comedones because barrier

dysfunction is accompanied by hyperkeratosis of the follicular epithelium.[38]

Conclusion

Acne is a disorder of childhood and adolescence, and increasing levels of circulating androgens of adrenal and gonadal origin seem to trigger the condition. The pathophysiology of acne includes, in a somewhat sequential manner, retention hyperkeratosis, sebaceous gland hyperplasia and increased sebum production, colonization of the follicles by *P acnes*, and perifollicular inflammation. The goals of therapy are to reverse these pathogenetic events and thereby minimize or prevent acne lesions.

Part 2 of this article will discuss treatment options for children and adolescents based on the pathophysiology of acne.

REFERENCES

1. Ebling FJ, Cunliffe WJ. Disorders of the sebaceous glands. In: Champion RH, Burton JL, Ebling FJ, eds. *Textbook of Dermatology*. 5th ed. Oxford, England: Blackwell Scientific Publications; 1992:1699-1744.
2. Street ME, Weber A, Camacho-Hubner C, et al. Girls with virilisation in childhood: a diagnostic protocol for investigation. *J Clin Pathol.* 1997;50:379-383.
3. Roberts J, Ludford J. Skin conditions of youths 12-17 years. data from the National Health Survey, 1966-1970. *Vital Health Stat 1*. 1976;11:1-66.
4. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. *Vital Health Statistics*. 1999;10(200):1-212.
5. Lobo RA. Hirsutism, alopecia, and acne. In: Becker KL, Bilezikian JP, eds. *Principles and Practice of Endocrinology and Metabolism*. 2nd ed. Philadelphia, Pa: JB Lippincott Williams & Wilkins; 1995:924-940.
6. Kelly AP. Acne and related disorders. In: Sams WM Jr, Lynch PJ, eds. *Principles and Practice of Dermatology*. 2nd ed. New York, NY: Churchill Livingstone; 1996:801-818.
7. Landow K. Dispelling myths about acne. *Postgrad Med*. 1997;102:103-112.
8. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med*. 1997;336:1156-1162.
9. Brown SK, Shalita AR. Acne vulgaris. *Lancet*. 1998;351:1871-1876.
10. Cunliffe WJ, Holland DB, Clark SM, et al. Comedogenesis: some new aetiological, clinical and therapeutic strategies. *Br J Dermatol.* 2000;142:1084-1091.
11. Toyoda M, Morohashi M. New aspects in acne inflammation. *Dermatology*. 2003;206:17-23.
12. Webster GF. Acne vulgaris. *BMJ*. 2002;325:475-479.
13. Koreck A, Pivarcsi A, Dobozy A, et al. The role of innate immunity in the pathogenesis of acne. *Dermatology*. 2003;206:96-105.
14. Webster GF. Acne vulgaris: state of the science. *Arch Dermatol*. 1999;135:1101-1102.
15. Thiboutot D. Hormones and acne: pathophysiology, clinical evaluation, and therapies. *Semin Cutan Med Surg*. 2001;20:144-153.
16. Akimoto N, Sato T, Sakiguchi T, et al. Cell proliferation and lipid formation in hamster sebaceous gland cells. *Dermatology*. 2002;204:118-123.
17. Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. *Endocr Rev*. 2000;21:363-392.
18. Stewart ME, Downing DT, Cook JS, et al. Sebaceous gland activity and serum dehydroepiandrosterone sulfate levels in boys and girls. *Arch Dermatol.* 1992;128:1345-1348.
19. Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Wilson JD, Foster DW, Kronenberg HM, et al, eds. *Williams Textbook of Endocrinology*. 9th ed. Philadelphia, Pa: WB Saunders Company; 1998:1509-1625.
20. Eady EA, Cove JH. Is acne an infection of blocked pilosebaceous follicles? implications for antimicrobial treatment. *Am J Clin Dermatol.* 2000;1:201-209.
21. Leyden JJ. The evolving role of *Propionibacterium acnes* in acne. *Semin Cutan Med Surg*. 2001;20:139-143.
22. Kim J, Ochoa M-T, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol*. 2002;169:1535-1541.
23. Webster GF. Inflammatory acne represents hypersensitivity to *Propionibacterium acnes*. *Dermatology*. 1998;196:80-81.
24. Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspectives. *J Invest Dermatol*. 2002;119:992-1007.
25. Hoffmann R. Enzymology of the hair follicle. *Eur J Dermatol*. 2001;11:296-300.
26. Cunliffe B. Acne. diseases of the skin and their treatment: *Pharmaceut J*. 2001;267:749-752.
27. Mercurio MG, Gogstetter DS. Androgen physiology and the cutaneous pilosebaceous unit. *J Gend Specif Med*. 2000;3:59-64.
28. Imperato-McGinley J, Gautier T, Cai LQ, et al. The androgen control of sebum production. studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. *J Clin Endocrinol Metab*. 1993;76:524-528.
29. Lucky AW, Biro FM, Simbartl LA, et al. Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. *J Pediatr*. 1997;130:30-39.
30. Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol*. 2001;116:793-800.
31. Jakubovic HR, Ackerman AB. Structure and function of skin. In: Moschella SL, Hurley HJ, eds. *Dermatology*. 2nd ed. Philadelphia, Pa: WB Saunders Company; 1985:1-74.
32. Proksch E, Holleran WM, Menon GK, et al. Barrier function regulates epidermal lipid and DNA synthesis. *Br J Dermatol*. 1993;128:473-482.

33. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. *Adv Lipid Res*. 1991;24:1-26.
34. Hanley K, Rassner U, Jiang Y, et al. Hormonal basis for the gender difference in epidermal barrier formation in the fetal rat: acceleration by estrogen and delay by testosterone. *J Clin Invest*. 1996;97:2576-2584.
35. Kao JS, Garg A, Mao-Qiang M, et al. Testosterone perturbs epidermal permeability barrier homeostasis. *J Invest Dermatol*. 2001;116:443-451.
36. Downing DT, Stewart ME, Wertz PW, et al. Essential fatty acids and acne. *J Am Acad Dermatol*. 1986;14:221-225.
37. Melnik B, Kinner T, Plewig G. Influence of oral isotretinoin treatment on the composition of comedonal lipids: implications for comedogenesis in acne vulgaris. *Arch Dermatol Res*. 1988;280:97-102.
38. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. *Arch Dermatol Res*. 1995;287:214-218.

DISCLAIMER
The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

FACULTY DISCLOSURE
The Faculty Disclosure Policy of the Albert Einstein College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the activity. Any discussions of unlabeled or investigational use of any commercial product or device not yet approved by the US Food and Drug Administration must be disclosed.