Acne Vulgaris: Recent Advances in Pathogenesis and Treatment

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Hormonal factors, particularly androgens, appear to be important in the pathogenesis of acne vulgaris. The sebaceous glands in acne are more sensitive to normal blood levels of androgens, and are stimulated to produce more sebum. Corynebacterium acnes in the sebaceous follicles act on triglycerides in the sebum to form free fatty acids which might alter the process of keratinization in the follicular canal. A microcomedo is formed which can progress to the clinical lesions of acne. Sebum and its components may also be inflammatory if released into the skin. There are, however, still a number of unanswered questions relating to acne pathogenesis. Currently, therapy of acne vulgaris revolves around topical benzoyl peroxide and retinoic acid and systemic tetracyclines. Benzoyl peroxide and tetracyclines are antibacterial while retinoic acid is comedolytic. Because of these different actions, combined therapy appears to be more effective (benzoyl peroxide and/or tetracyclines together with retinoic acid). Topical antibiotics show promise as new therapeutic agents.

This is a brief review of current thoughts on the pathogenesis and treatment of acne vulgaris. A large amount of information has been accumulated about pathogenesis, some of which is probably irrelevant or misleading. Consequently, the hypothesis of the pathogenesis of acne which is postulated here remains just that – an hypothesis.

Heredity

Other than the observation that individuals with severe acne often have a family history of severe acne and a study in 1958 that demonstrated 98 percent concordance of acne in identical twins,[1] little is known about the genetics of acne. It is such a common disorder (Kligman believes that the prevalence is 100 percent in adolescents[2]) that it becomes difficult to study the inheritance adequately. Acne is probably polygenic in origin and the sum of the action of many genes produces the phenotypic expression which is then modified by external factors.

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Diet

Under normal circumstances, dietary factors are probably of no importance in the pathogenesis of acne. There is no evidence that high carbohydrate or fat intake increases the output of sebum or alters its composition. Fulton et al[3] gave acne patients a special chocolate bar containing ten times the average amount of chocolate with no significant effect.

Endocrine Factors

Androgens[4]

Sebaceous glands are very sensitive to androgenic stimulation. At birth the glands are often enlarged – probably due to maternal androgens. During most of childhood they are small and virtually nonfunctioning, but if androgens are administered, enlargement occurs and acne may develop. Severe acne had been known to occur in preadolescents with aplastic anemia treated with androgenic steroids.

Males produce ten times more testosterone than females, and males also produce more sebum than females. In males the glands are normally maximally stimulated and no increase in sebum production occurs after testosterone administration. If testosterone is administered to females, the sebaceous glands enlarge and more sebum is produced. The sudden appearance of anything more than mild acne in an adult female should, therefore, alert one to the possibility of a masculinizing syndrome.

There appears to be no increase in plasma androgens in acne patients as compared to controls.[5] The sebaceous enlargement and increased sebum production found in acne may be due to increased end-organ sensitivity, ie, the sebaceous glands have increased

sensitivity to normal blood levels of androgen. For greatest activity, testosterone must be converted to 5-alpha dihydrotestosterone by 5-alpha reductase. A recent report[6] indicates that acne skin performs the conversion 2 to 20 times greater than the corresponding normal skin. This might explain the increased sensitivity of acne patients' sebaceous glands to androgenic stimulation, but it may just reflect the fact that sebaceous glands are larger and more active in acne patients. Recently, a group of individuals has been reported who have a deficiency of 5-alpha reductase. They lack severe secondary male sexual characteristics and also do not develop acne.[7]

Estrogen[4,8,9]

There is no evidence that physiological levels of estrogen have any effect on sebaceous gland activity. Pharmacological doses of estrogen and contraceptive pills with high levels of estrogen have been shown to reduce sebum production. Estrogens applied topically to one side of the forehead produce a decrease in sebum production, but, since this also occurs on the untreated side, a systemic rather than a topical effect is suggested. If adequate amounts of androgen are available to the peripheral tissue, estrogens do not suppress sebum production.

Progesterone[9,10]

Physiological or pharmacological doses of progesterone do not appear to influence sebaceous gland activity, but synthetically altered steroidal compounds with progestational activity do stimulate sebaceous glands. These are 10-nortestosterone derivatives and they probably retain their androgenic properties. They are used as components of contraceptive pills.

The clinical significance of the estrogen and progesterone effects is that the high estrogen pills, which are less used today, tend to improve acne, whereas low estrogen pills may make acne worse.

Pituitary Hormones[11,12]

Experimental evidence suggests that ACTH, gonadotrophin, and thyroid-stimulating hormone (TSH) are necessary to maintain full sebaceous gland activity, probably via hormones produced by their respective target organs. However, sebum production falls and remains low with pituitary failure even with replacement of testosterone, thyroxine, and hydrocortisone. This suggests the production of a separate "sebotrophic hormone." It has been proposed that the posterior pituitary hormone, beta melanin stimulating hormone (MSH) is also the sebotrophic factor. However, Thody et al[13] could not show increased beta MSH levels in acne patients with increased sebum production. Beta lipotrophin, an anterior pituitary hormone, has also been proposed as having sebotrophic activity.[14] Growth hormone has also been investigated.[12] Sebum excretion rates and acne are both increased in acromegaly but the effect on the sebaceous glands might be nonspecific and due to the general somatrophic effect of growth hormone. Problems in this particular area are far from solved at this stage.

Adrenocortical Hormones

Adrenal androgens appear to contribute significantly to sebaceous gland development.[8] The administration of dehydroepiandrosterone and delta-4-androstenedione, two potent adrenal androgens, stimulates sebum production.[15] Adult male castrates have a low sebum production rate, although it is higher than in normal children who do not produce adrenal androgen. The administration of prednisone to castrated males causes a reduction in sebum production due to adrenal suppression. This does not occur in normal males who produce gonadal testosterone.[16] The autogenous glucocorticoid (hydrocortisone) does not show sebum stimulation[9] but it may have a permissive action to allow testosterone to exert its full effect.[17] The oral or topical administration of potent corticosteroids which may produce so-called "steroid acne" does not normally increase sebum secretion. These adrenal corticosteroids potentiate the ability of sebaceous follicles to develop hyperkeratosis and also augment the action of testosterone on androgen-sensitive tissues[17] – and this is probably how steroid acne is produced.

Bacterial Factors

The three main organisms found on the face are (1) Corynebacterium acnes (Propionibacterium acnes), (2) Staphylococcus epidermidis, and (3) the yeast-like Pityrosporum ovale and P. orbiculare.[18]

It is presumed that organisms play a role in acne by elaborating lipases which split the triglycerides in sebum to free fatty acids (which have been strongly implicated in the pathogenesis of acne).[19] Marples[18] has shown in vivo that only C. acnes is of importance in this regard. Voss[20] has taken a slightly different approach and suggests that sebum is a selective substrate for growth of bacteria and that products of this bacterial growth including lipases, free fatty acids and other enzymes, toxins, irritants, and antigens all act on the follicular epithelium to produce irritation and inflammation.

Sebum

Sebum plays an important role in the pathogenesis of acne. Sebaceous gland activity is significantly increased in acne subjects and the individuals with the most severe acne have the highest sebum secretion rates.[21] It has been shown that sebaceous gland lipid is composed of about 60 percent triglycerides, 25 percent wax esters, and 15 percent squalene.[22] As sebum is carried to the skin surface through the pilosebaceous canal, partial lipolysis of triglycerides occurs with the formation of free fatty acids. C. acnes appears to be important in this respect by producing lipase.

Sebum seems to play a role in producing both the inflammatory and noninflammatory lesions of acne. Using the rabbit ear experimental model[23] sebum was found to be comedogenic which suggests, but does not prove, that sebum has similar properties on human skin. Free fatty acids seem to be more comedogenic than other fractions of sebum. A study in 1965,[24] in which sebum or its components were injected into human skin, showed that whole sebum produced inflammatory changes, but isolated free fatty acids produced even greater inflammation. However, in a recent study[25] the amounts of free fatty acids in pilosebaceous glands in acne were first determined and this amount then injected. Minimal inflammation was produced. These workers suggest that the inflammatory changes

produced in the earlier study were related to much higher amounts (nonphysiological) of injected free fatty acids.

Tetracyclines, widely used in the treatment of acne, produce a reduction of free fatty acids by decreasing the population of C. acnes and possibly also by inhibiting bacterial lipase.[26] Benzoyl peroxide has also been shown to decrease the numbers of C. acnes and to reduce the amount of free fatty acids. However, recent work[27,28] has shown that application of lipase inhibitors to skin with a dramatic reduction of free fatty acids does not produce any improvement in the acne. These two recent studies introduce some doubts about the true importance of free fatty acids in the pathogenesis of acne.

Studies on skin surface lipid composition in patients with acne as compared to controls have produced conflicting data.[29] Acne patients appear to have higher squalene levels than controls, and squalene has been shown to be comedogenic.[23] Some studies have shown low surface free fatty acid levels in severe acne,[29] again casting some doubts on the significance of free fatty acids in acne.

Pilosebaceous Follicles and Comedones

Acne is a disease of sebaceous follicles of the face, chest, back, and upper arms. Follicles affected by acne have a very small pilary portion with tiny hairs and very large sebaceous glands which drain into a wide canal. The comedo is the primary lesion of acne. It is an impaction of horn cells within pilosebaceous follicles. Kligman[17] classifies comedones as either primary or secondary.

Primary

These start as microscopic comedones (microcomedones) which develop into closed comedones or whiteheads. Closed comedones are small (1 to 2 mm), whitish papules resembling milia. The openings of the follicles in closed comedones are minute and generally cannot be seen. Closed comedones in turn evolve either into open comedones (blackheads) or inflammatory papules. Primary comedones are thus microcomedones, closed comedones, and open comedones.

Secondary

These result from the rupture and reencapsulation of primary comedones. They are larger and tend to have irregular shapes. An acne cyst is an example of a polyporous, clustered comedo.

The first change observed[30] in the development of the comedo occurs in the so-called infra-infundibulum of the follicle. This region usually produces only a thin horny layer which sloughs rapidly. At the onset of comedo formation a granular layer is observed and a much thicker and cohesive horny layer is formed. These horn cells tend to stick together to form a compact mass, the microcomedo. Why this change occurs is unclear but it has been suggested that the intercellular cement that normally binds the cells together is altered in some way and a more permanent bond is formed. There also appears to be an increased production of horn cells in the infra-infundibulum. The combination of increased adhesiveness and retention of the cells and the increased production contribute to the formation of comedones.

Since the primary change occurs in the infra-infundibulum, the comedone is formed beneath the surface and is not visible on the surface. It is thus a closed comedone and appears clinically as a small noninflammatory papule, the whitehead. Closed comedones tend to continue to produce horn cells and either rupture or produce infra-infundubula opening to produce open comedones or blackheads.

Closed comedones do not allow sebum or debris to drain and are more likely to rupture. Open comedones, however, appear to have channels within them allowing sebum to drain. Even though sebaceous glands become atrophic when comedones form, they still secrete sebum. With rupture of closed comedones, sebum leaks out and presumably incites an inflammatory response. With open comedones, sebum is able to drain and inflammatory lesions are less likely to occur.

Much disagreement exists regarding the various steps of comedone formation. It is suggested that the sebaceous glands are stimulated to produce adult amounts of sebum. C. acnes acts on the triglycerides of the sebum to form free fatty acids which alter the process of keratinization in the follicular canal. A closed comedo results which either becomes an open comedo or an inflammatory lesion. Sebum and free fatty acids appear to play a role in inciting the inflammatory reaction leading to the formation of pustules and cysts. This whole scheme is only an hypothesis and other factors are probably also of great importance.

Recent Advances in Therapy

At this time, therapy of acne vulgaris consists primarily of various combinations of benzoyl peroxide, retinoic acid, and systemic tetracyclines. Topical antibiotics show promise as new therapeutic agents.

Benzoyl Peroxide

Benzoyl peroxide has antibacterial properties. Its topical application causes excellent suppression of C. acnes with virtual eradication of the organism after two weeks of therapy (5 percent benzoyl peroxide applied twice daily).[31] There is a corresponding decrease of free fatty acids by about 50 percent. Benzoyl peroxide is also comedolytic.[31] Daily application of 5 or 10 percent benzoyl peroxide for two weeks reduces the size of rabbit ear comedones by about 50 percent. Benzoyl peroxide thus has a dual mechanism of action, antibacterial and comedolytic. Therapy is usually begun with 5 or 10 percent applied at night and increased to more frequent daily applications. It has recently been recommended[32] that the strength of benzoyl peroxide be increased to 20 percent (or 20 percent with 10 percent sulfur) especially for acne of the back and chest. Sulfur has fallen into some disrepute as it has been shown to be comedogenic,[33] although this has been disputed.

Retinoic Acid[31]

The two main actions of retinoic acid which make it so useful in acne vulgaris are:

1. It loosens cell attachments: horn cells do not stick together to form impactions, and comedo formation is prevented.

2. It stimulates mitotic activity of the follicular epithelium: existing comedones tend to be expelled and closed comedones are more rapidly transformed into open comedones.

Treatment is started with the 0.05 percent cream applied on alternate nights. If no excessive redness and irritation develops, applications can be increased to nightly. Both the physician and the patient should be aware of the manufacturers' instructions regarding the use of retinoic acid, and with care, irritation can be reduced to a minimum.

Combined Benzoyl Peroxide-Retinoic Acid Therapy[30]

Because retinoic acid and benzoyl peroxide have different actions, their combined use has been suggested. It seems that combined treatment reduces C. acnes and free fatty acids to a greater extent than benzoyl peroxide alone. The mechanism may be that retinoic acid makes skin more permeable which increases the tissue concentration of benzoyl peroxide. One regimen is to start with benzoyl peroxide applications in the morning and to add the retinoic acid several weeks later in the evening.

Systemic Tetracyclines

The tetracycline group of antibiotics is the most widely used but other antibiotics may also be used, eg, erythromycin. With tetracycline, the population of C. acnes is decreased by 90 percent or more and the proportion of free fatty acids in the surface lipid falls by about 50 percent. The combined use of systemic tetracyclines and topical retinoic acid, which have different modes of action, has been shown[34] to yield results superior to those of either drug used alone.

A recent report[35] concerns the use of high-dose tetracycline in acne. The patients had severe treatment-resistent acne and were given 2 gm of tetracycline daily for 3 to 33 months. Of the 31 patients, 14 cleared and 13 improved greatly. Side effects did occur but the drug had to be discontinued in only three patients.

Topical Antibiotics

In 1974, Fulton and Pablo[36] reported the results of their investigation using topical antibiotics in the treatment of acne. The erythromycin group in a simple vehicle reduced the free fatty acid level and improved inflammatory lesions. Other workers confirmed the clinical effectiveness of topical erythromycin (2 percent).[37]

Topical clindamycin has also been found to be effective.[38] Tetracycline has also been used topically and found to be as effective as oral tetracycline[39] at a 0.5 percent concentration. Similar results have been obtained in a multigroup study.[40] Work with all topical antibiotics in acne is still experimental.

Estrogens[30]

Estrogens are still used in treating moderate to severe cystic acne in women. The most widely used contraceptive pills contain 50 μg of estrogen, which usually suppresses sebum production in most individuals. The very low estrogen pills do not suppress sebum production and higher estrogen pills increase the potential hazards of estrogen. Estrogens should be reserved only for a relatively small group of female patients with relatively severe cystic acne which has not responded to adequate trials of standard therapy. On contraceptive pills, sebum output decreases slowly and is rarely more than a 50 percent decrease. The beneficial effect is seen only after some months; about one third of patients fail to respond and others may relapse while still on the contraceptive pill.

Antiandrogens

It would seem logical to use antiandrogens in the therapy of acne vulgaris. At present the work is entirely experimental. The major problem, assuming that an effective antiandrogen can be developed, is to limit its effect to sebaceous glands.

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