Acne Vulgaris

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Acne vulgaris displays all the characteristics of a polygenic disorder in that hereditary factors are apparent with strong family tendencies for the disorder while the phenotypic expression of the disease varies over a wide spectrum. All that is known for certain concerning the genetics of acne is that concordance is extremely high in identical twins.[1] In the past decade, various investigations have resulted in much clearer concepts of pathogenesis and have brought us to the point of effective therapy for the majority of cases. In this report, I will summarize recent concepts in the pathogenesis of acne vulgaris.

I. Acne Histopathogenesis.

The histopathogenesis of acne involves two main pathways: 1) impaction and distension of sebaceous follicles by tightly packed horny cells and 2) disruption of the follicular epithelium allowing discharge of the follicular contents into the dermis which then induces an inflammatory reaction.[2] The clinical counterparts of this process range from the non-inflammatory comedo to inflammatory papules, pustules, and nodules.

The sine qua non of acne is the formation of comedones. Ordinarily the epithelium lining the canal of sebaceous follicles produces keratinized cells which are sloughed and carried to the surface in a stream of sebum. Comedo formation begins when follicular horny cells begin to stick together. As horny cells fail to dehisce, an expanding solid mass accumulates and dilates the follicle. Recent electron microscopic study of the dynamics of comedo formation confirmed these observations and also demonstrated a decrease in lamellar granules (membrane coating granules, Odland bodies).[3] A decrease in membrane coating granules with comedo formation suggests that these structures may act as lysozymes and promote cell separation and not function to keep cells together as "cementsomes" as proposed by Hashimoto.[4] Further studies on the dynamics of comedo formation and the ultrastructural changes which result in failure of separation of horny cells are needed. The developing comedo surfaces clinically first as a "whitehead" in which the surface opening is microscopic and then bulges above the skin surface as a "blackhead." The color is due to melanin pigment produced by melanocytes which are found in the upper 20% of sebaceous follicle epithelium.[5]

A mature comedo is thus several millimeters deep and firmly entrenched. Attempts to dislodge these lesions by vigorous, abrasive washing in humans and in experimentally induced lesions in the rabbit ear model fail dismally. The significance of this area of research to the clinician is that vigorous washing is of little use in acne therapy. Former concepts of obstruction at the follicular outlet which could be relieved by frequent washings and use of "peeling" agents were grossly incorrect. Such theories do not stand up to the overwhelming evidence that comedones represent an impaction of the follicular canal with a solid mass of horny cells. Comedones are deep structures and successful therapy can only be achieved by altering the abnormality in follicular keratinization. Retinoic acid's mechanism of action involves its effect on keratinization. As a side effect, it can produce "peeling" and dryness, but this is unrelated to its mode of action. In the treatment of both experimentally induced comedones and naturally occurring lesions, retinoic acid induces the formation of horny cells which no longer stick together.[6] Inhibiting

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the synthesis or quality of the cement substance which binds horny cells into solid impactions thus attacks the disease at the very point of origin.

Acne becomes an inflammatory process when the comedo ruptures. Disruption of the follicular wall may be partial or complete. The severity of the clinical lesion correlates directly with the extensiveness of the rupture and ranges from a segmental disorganization of follicular epithelium, resulting in a quick-healing pustule, to major breakdowns and dissolution and formation of a deep indolent nodule.

Rupture is not a consequence of simple pressure. Neutrophils first collect along the border of the follicle, usually in a circumscribed fashion, and then invade the epithelium, inducing spongiosis and cellular degeneration and finally rupture of the follicular epithelium.[2] A dermal abscess consisting first of leukocytes and later mononuclear cells and giant cells then develops. Partial ruptures heal by resorption and the horny impacted mass remains in situ. In moderate-sized ruptures, the severed ends of epithelium send out sheets of undifferentiated cells which undermine and reincapsulate the abscess analogous to the healing processes involved in superficial wounds. A new epithelial lining is formed and redifferentiates into a keratinizing membrane and produces coherent horny cells. With repeated breaks and repair, secondary comedones develop which are recognizable clinically because they have irregular shapes and sizes and can mimic small keratinous cysts.[2]

Massive rupture of developing comedones results in the follicular contents being literally extruded into the dermis, and a violent inflammatory reaction results which is seen clinically as a tender, erythematous papule or nodule. These lesions are deep and can persist for weeks as a foreign body granuloma replaces the initial abscess.[2]

The significance of these insights in the pathogenesis of inflammatory lesions rests in the fact that pustules, papules, and nodules actually represent an *inflammatory* process and not an infectious one despite the similarity of the lesions to pustules and furuncles caused by *Staphylococcus aureus (S. aureus)*. The fact that an acne nodule represents an inflammatory process accounts for the benefit of intralesional corticosteroid therapy. If these lesions were infections, steroid injection would surely worsen the condition. Similarly, appreciation that papules, pustules, and nodules are inflammatory reactions to extruded follicular material is important when evaluating antibiotic therapy in acne. Antibiotics do not induce pustules and papules to resolve. Rather they work in an indirect way to minimize formation of new lesions.

II. Bacteria and Acne.

It has long been recognized by clinicians that systemic antibiotics are beneficial in the therapy of inflammatory acne, but it is not until relatively recently that the role of bacteria has been studied.

Three kinds of organisms are constantly found in the sebaceous-rich areas and they constitute the normal resident microflora of all persons, regardless of the presence or absence of acne.[7] They include: 1) the yeast Pityrosporun; 2) aerobic coagulase negative cocci; and 3) the anaerobic diphtheroid now officially classified as *Propionibacterium acnes* (*P. acnes*). The aerobic cocci and Pityrosporun are mainly located superficially near the orifices of sebaceous follicles. *Propionibacterium acnes* inhabits the depths of the follicle and there is considerable evidence implicating this organism in the pathogenesis of inflammatory acne.

1. Large numbers of *P. acnes* accumulate in follicles immediately preceding comedo formation.[2]
2. Acne subjects have significantly greater numbers of *P. acnes* than aged-matched controls. This difference is present in those between 11 and 20 years of age, but does not exist in older individuals.[8]
3. *P. acnes* produces substances capable of inducing comedo formation in the rabbit ear model.[2]
4. *P. acnes* is responsible for the liberation of free fatty acids which are comedogenic and capable of inciting pronounced inflammatory reactions.[9,10]
5. In the absence of *P. acnes*, inflammatory lesions are not seen. Comedones provoked in the rabbit ear never rupture because they are sterile; coal tar and chloracne are predominantly comedonal. The antimicrobial activity of those agents prevents the development of inflammatory lesions.[2]
6. Antibiotics such as tetracycline and erythromycin which suppress *P. acnes* are beneficial in therapy, while others such as penicillin and sulfonamides do not effect *P. acnes* population and are ineffective in acne therapy.[11]
7. Prolonged antibiotic therapy also appears to

eventually result in a decrease in comedones.[12]

Studies to date thus have implied that a normal resident organism is acting somehow to promote the follicular rupture and subsequent inflammatory reaction which results in clinical papules, pustules, and nodules. The mechanisms by which *P. acnes* induces inflammatory lesions is still to be settled. The significance of free fatty acid production has recently been seriously challenged by the finding that a topical lipase inhibitor suppressed free fatty acid formation, yet the clinical disease was unaffected.[13] However, *P. acnes* also possesses a variety of other enzymes including hyaluronidase which may be more significant in the disruption of the follicular epithelium that leads to an inflammatory lesion.

Further studies in our laboratory indicate that *P. acnes* appears incapable of developing resistance to tetracycline and erythromycin. This is of importance when evaluating a patient whose acne is not responding as favorably as expected to systemic antibiotics. *Propionibacterium acnes* resistance does not explain resistant cases. Some patients, however, can have significant impairment of intestinal absorption if they ingest antacids or large quantities of milk.

There are two useful techniques for documenting poor absorption of antibiotics. The easier technique involves the use of a Wood's light. *Propionibacterium acnes* makes a coproporphyrin which fluoresces coral red under Wood's light examination. During antibiotic therapy, the intensity of this fluorescence is markedly decreased and often completely eliminated. The nose and nasolabial folds are the areas of maximum fluorescence and easiest to examine. If these areas still fluoresce heavily after a month of systemic antibiotic therapy, then incomplete intestinal absorption of the antibiotic is likely. The second technique involves measurement of the degree of resistance of the surface aerobic flora to the antibiotic a patient is taking. Normally the surface aerobic cocci show little (less than 20%) resistance to tetracyclines, erythromycin, and clindamycin. After two to three weeks of therapy, approximately 80% of the surface aerobic flora will be resistant to a systemically administered antibiotic.[11] By quantitatively culturing the surface aerobic flora on media with and without added antibiotics, one can rapidly estimate the degree of resistance. If the antibiotic has not been absorbed, the surface flora will not have developed a high degree of resistance. Quantitative cultures provide precise data, but even semi-quantitative analysis, easily done by any laboratory, gives sufficient data to document whether or not a particular patient has a problem in absorption of an antibiotic.

These two techniques can therefore be used to determine rationally whether a change in antibiotic therapy is indicated rather than blindly switching from one agent to another.

For twenty years, successful antibiotic therapy in acne has been limited to systemic agents. More recently, as basic information has accumulated on the factors involved in percutaneous penetration, the age of topical antibacterial therapy has arrived. Agents are now available which can penetrate sebaceous follicles sufficiently to suppress *P. acne*. Benzoyl peroxide is now available in several formulations and has been shown to effectively suppress *P. acne* and to be effective in the control of inflammatory acne.[14] More recently, 2% erythromycin has been shown to exert a similar beneficial effect. Unquestionably, several other agents, formulated to penetrate skin, will be forthcoming. While the use of systemic antibiotics in acne has proved to be unusually free of serious side effects, the future on antibacterial therapy in acne lies in effective topical agents.

III. Sebum Production and Acne.

Acne and excessive production of sebum are inseparable. While there is some individual overlap, acne patients have a greater mean sebum production than age- and sex-matched controls.[15] Furthermore, the severity of the disease parallels sebum production—an absolute characteristic of acne conglobata is excessive oiliness. Acne does not make its debut until pre-puberty when sebaceous glands start to enlarge under the influence of adrenal hormones. This prepubertal onset of acne coincides with enhanced supplies of cortisol and adrenal androgens accompanying adrenal gland maturation. Cortisol appears to act in a permissive fashion in two ways: 1) Corticosteroids are known to augment the action of testosterone on androgen-sensitive tissue,[16,17] 2) corticosteroids potentiate the follicles' ability to undergo retention hyperkeratosis and form comedones.[2] With the onset of gonadal function and testosterone production, a further increase in sebum secretion occurs and acne severity increases. While adrenal and gonadal hormones are prerequisite to development of sebaceous gland size and function, all studies indicate that acne patients have normal circulating levels of androgenic hormones.[15] No difference exists even when the most severely afflicted are compared with appropriate control subjects. Enlarged sebaceous

glands and overproduction of sebum seem therefore to indicate an end-organ sensitivity. In fact a recent study does suggest that the sebaceous glands of acne patients metabolize testosterone to the metabolically more active dihydrotestosterone at a much greater rate than those of non-acne subjects.[18] Such a finding supports the hypothesis of end-organ sensitivity and explains why testosterone blood levels are not higher in acne patients. This study suffered, however, by not matching controls to sebum production, and until such studies are performed, the inviting concept of end-organ sensitivity to normal levels of testosterone is not yet proven. Future investigations of this end-organ hypersensitivity promise to reveal basic secrets of the acne process.

Currently, researches are being made for topically effective agents which act to produce a local suppression of sebum production. If an agent or agents can be found which are free of systemic effects, a major advance will have been made.

IV. Miscellaneous Factors.

Diet. No evidence exists to incriminate dietary factors. The few studies on this subject have all come to the conclusion that diet does not play a role.[19,20] Dietary restrictions do not constitute rational measures in an anti-acne regimen.

Friction and Trauma. Once one understands the evolution of an inflammatory lesion, the adverse effect of friction is apparent. Repeated trauma to a follicle, distended by an impaction of horny cells, promotes rupture of the follicular epithelium and the formation of new inflammatory lesions. The common sources of friction include overzealous washing, particularly with abrasive soaps, habits of leaning on or rubbing an area of the face, pressure from helmets, tight collars, wrestling, and other contact sports. At times, local physical factors can be severe enough to the degree that usually effective therapy appears at best to be merely containing the process instead of suppressing the formation of new inflammatory lesions. Failure to perceive the role of friction often leads the therapist to switch from one antibiotic to another in a fruitless search for the "best antibiotic."

Emotional Factors. While rigorously controlled studies with endocrinological monitoring have not been done, there is general agreement that emotional factors can play a significant role. The probable mechanism is the production of adrenal androgens which lead to increased seborrhea followed by crops of inflammatory lesions. Women appear to be more susceptible, possibly because their sebaceous glands are not as maximally stimulated as those of men and any increase in circulating androgens will have a proportionally greater effect. The ultimate expression of this factor occurs in women and is often referred to in texts as pyoderma faciale. Actually, this is an explosive form of acne almost exclusively seen in women. Classically, a severe emotional stress precedes the onset of marked seborrhea which is then rapidly followed by the onset of deep nodular and pustular lesions. This form of acne is extremely difficult to control, and in addition to the usual therapeutic maneuvers, some form of tranquilizer or sedation is necessary.

Ultraviolet Light. Most dermatologists would agree that ultraviolet light is helpful in acne therapy. Acne patients in general appear to improve in the summer. However, such improvement may more accurately reflect seasonal variation in the disorder which is unrelated to ultraviolet light. Recently, Kligman and Mills have incriminated ultraviolet light in that erythemic radiation actually enhances the comedogenic activity of materials such as coal tar and free fatty acids in both humans and in the rabbit-ear model.[21] Further work is needed in this area to discern just what happens to the acne patient who spends his summer on the beach and appears to improve and require less therapy.

Cosmetics. Many cosmetics including cleansing creams and moisturizers contain chemicals which can aggravate acne.[22] The mechanism appears to be that of inducing the derangement of keratinization which results in horny cells sticking together and eventual impaction of the follicle. Cosmetics do not produce a physical obstruction of the follicular orifice, rather the mechanism appears to be due to a chemical induction of comedo formation. The follicular epithelium is induced to form horny cells which stick together and eventually result in comedones.

Therapy.

With the basic concepts of pathogenesis as outlined above, our approach to acne therapy is as follows:

1. *Diet.* No evidence exists to substantiate the common belief that certain foods aggravate the acne process. Dietary restrictions are useless and ineffective.
2. *Skin care.* Acne patients are oily and want to remove the objectionable feel that excess oil produces. No "special soaps" are necessary. Patients should be instructed to wash *gently* two or three times daily to remove surface oil,

but under no circumstances should they scrub or abrade their skin. This leads to an intensification of the inflammatory aspects of acne. Blackheads are 4 mm deep and cannot be washed away—as most acne patients eventually discover. Local friction to the acne areas is to be avoided at all costs.

3. A primary and perhaps the central therapeutic maneuver involves the topical use of retinoic acid (Retin-A*) which reverses the abnormality in follicular keratinization. This material is applied once daily to the *entire* area of involvement, not just to clinical lesions. Application must be only to bone dry skin (no closer than 15 minutes to the last facial washing) to avoid unnecessary local irritation. Patients who also have atopic dermatitis may be able to apply this agent only once or twice a week. Retinoic acid unseats existing comedones in 8 to 12 weeks and prevents the formation of new lesions. As such it is the backbone of acne therapy. It is continued till the patient is free of new lesions for several months and then slowly withdrawn.
4. Antibiotics are indicated for patients who have moderate to severe inflammatory lesions. Tetracyclines and erythromycin have been time-proven safe and efficacious choices. The usual dose is 500 to 1,000 mg/day in divided doses initially and then gradual withdrawal as inflammatory lesions disappear. In combination with topical retinoic acid, most patients will not need antibiotics for more than 3 or 4 months. More recently, properly formulated topical antibiotics have been introduced. Currently, there are several formulations of benzoyl peroxide which are extremely effective. Many patients, however, cannot use both benzoyl peroxide and retinoic acid simultaneously because of excessive local irritation. More recently, 2% erythromycin free base has been shown to be effective, but it is not yet readily available.
5. If there is excessive emotional tension or pressure, then this too must be counteracted by a mild tranquilizer.
6. The excessive use of cosmetics especially moisturizers, cleansing lotions, and face creams should be discouraged.

The successful management of acne involves a careful detailing of the factors involved in pathogenesis to insure confidence and cooperation with the now quite successful therapeutic maneuvers available.

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