Systemic Agents in the Management Of Acne

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■ *Topical therapy including incision of pustules and injection of corticosteroids into nodular and cystic lesions remains the mainstay of the management of acne.*

Systemic agents, including diuretics, corticosteroids, broad spectrum antibiotics and progestin-estrogen combinations are significant and valuable additions to the therapy of resistant pustulocystic acne. They are, however, not without side effects and they should be reserved for carefully selected patients for whom they may, when used with discretion, produce gratifying results with relatively low risk.

UNDERSTANDING OF THE complex interrelationship among the various factors influencing the development of acne has improved with increased study of the fundamental pathogenesis of this common and intriguing disease. Despite this growing body of knowledge, therapy for acne remains to a great extent empiric, with the rationale for a given modality often following rather than preceding its use. For many years, topical therapy has remained the mainstay of the management of acne. Topical measures have included cleansing of the skin with a variety of agents, the application of an almost endless series of drying and peeling lotions which consist primarily of various combinations of sulfur, resorcin and salicylic acid, desquamation of the skin with carbon dioxide slush or ultra violet light, mechanical extraction of closed comedones (whiteheads), and open comedones (blackheads), incision and drainage of pustules and fluctuant cysts and, more recently, the injection of various corticosteroids directly into non-fluctuant cystic and nodular lesions.

Such measures, although tedious and time-consuming, have often provided good control of this eventually self-limiting disease while waiting for the active process to become quiescent. However, the more severe and disfiguring forms of pustular and cystic acne with their sometimes disastrous emotional impact on the developing teen-age boy or girl and their severe residual scarring, both physical and psychological, have often eluded control with topical agents alone. Although the use of dermabrasion has been partially successful in reversing the permanent scarring changes following upon severe pustulocystic acne, a far more preferable approach is prevention of the scarring by adequate control of the original disease process.

The development of several newer means of systemic therapy has helped improve the management of these more severe forms of the disease. Most significant among them is the long-term administration of chemotherapeutic agents, particularly the broad spectrum antibiotics, and the use of

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estrogen-progestin combinations either together or sequentially. Before proceeding to a more detailed consideration of these agents, I would like to comment briefly on the influence of other systemically administered agents in the management of acne.

Diet

In a broad sense, alterations in diet may be considered as systemic therapy, and in the management of acne there is a long list of dietary restrictions that have been proposed at various times, including such foods as chocolate, cheese, milk, nuts, fats, carbohydrates, shellfish. Although many dermatologists still incriminate chocolate[32] as an offender, there is growing acceptance for the view expressed by Hopkins in 1958[21] that "We have no reliable evidence that the food one eats has anything to do with outbreaks of acne . . .," and it would seem unnecessary at this time to impose dietary restrictions on most patients with acne.

Vitamin A

Although a venerable member of the anti-acne armamentarium, vitamin A has never been unequivocally shown to be of value in the management of any form of acne, and a recently carefully controlled double-blind study[1] comparing the results of vitamin A administered orally in a dose of 150,000 units daily for 12 weeks and a lactose placebo, revealed no difference in effectiveness between the two. An important point emphasized in this study was the difficulty of accurately assessing the influence of treatment on the course of acne by clinical impression alone. The more objective evidence provided by serial photographs compared by a panel of qualified observers at a later date proved more accurate and reliable, and at the same time highlights the difficulty of making objective reproducible clinical assessments in a therapeutic trial in a disease subject to spontaneous exacerbation and remission. There does not seem to be a firm place for vitamin A in the management of acne at this time.

Diuretics

Many female patients are noted to have a flaring of acne during five to 10 days preceding the onset of menses. These patients often also have a gain in weight during the same time.[31] Since it is known that there is no alteration in sebum production during the various phases of the menstrual cycle,[31] it would seem reasonable to postulate a possible relationship between premenstrual retention of fluid and exacerbation of acne. And indeed in many such patients the administration of a diuretic during a period of from five to 14 days before menses has proven effective in eliminating or decreasing the severity of these premenstrual flares. The thiazide diuretics are widely used for this purpose, although any effective diuretic well tolerated by the patient should be equally effective. Double-blind studies are needed for final evaluation of this modality.

Corticosteroids

Although corticosteroids may themselves produce a papulopustular follicular acneform eruption, they do appear to have an effective role in reducing the inflammatory lesions of severe cystic acne. However, double-blind studies are also needed here. Because of the hazardous side effects associated with corticosteroid administration, use of them should be reserved for selected severe cases of cystic acne with extensive involvement unresponsive to other modes of therapy. Treatment should be of the shortest duration possible, with a suggested initial daily oral dose in the range of 20 to 30 mg of prednisone or its equivalent, with gradual withdrawal preferably within a month or so, although in exceptional cases long-term treatment may be necessary, with its concomitant increase in risk of side effects.

Chemotherapeutic Agents

Since Andrews[2] reported the successful use of systemically administered antibiotics in the management of acne in 1951, a number of studies* have been published reporting the good therapeutic results obtained in the management of pustular and cystic acne by use of a variety of antibiotics and sulfonamides. These have included several controlled double-blind studies.[20,40,49] Such double-blind studies are especially important in evaluating therapy in a disease such as acne which is subject to repeated spontaneous exacerbations and remissions. Most of the recent interest in antibiotic therapy for pustular and cystic acne has centered around the tetracyclines,† and it is with this family of broad spectrum antibiotics that the remainder of this discussion will be concerned.

Although, as noted previously, a number of uncontrolled studies have been reported demonstrating the value of the tetracyclines in pustular and cystic acne, there has been some conflict of opin-

*Reference Nos. 4, 9, 10, 11, 20, 22, 40, 45, 46, 49.
†Reference Nos. 9, 10, 12, 16, 20, 31, 38, 39, 40, 49.

ion as to their value expressed in several recent controlled studies.

Hicks,[20] Stewart[40] and Wansker[49] have all published double-blind controlled studies showing the apparently unequivocal value of orally administered tetracyclines in many patients with pustulocystic acne. The matched placebo-treated and tetracycline-treated patients studied by Freinkel and coworkers[16] showed similar clinical results, and in both groups a reduction in free fatty acids of the surface lipids paralleled clinical improvement. On the other hand, Smith and coworkers[34] in England and Crounse[12] here in the United States both failed to find any significant differences between placebo and tetracyclines in controlled double-blind studies of the treatment of acne. The general preponderance of opinion, however, favors the tetracycline group of broad spectrum antibiotics as active and useful agents in the management of pustulocystic acne.

In view of some disagreement as to their efficacy on the one hand and, on the other, their apparent ability to control severe pustulocystic acne with very small doses over a long period, it is of interest to inquire into the mechanism by which the tetracyclines exert their apparently favorable effect. Although the precise and final answer to this question is not yet known, a fairly convincing web of circumstantial evidence has been developed which points strongly toward at least one probable mode of action.

In general, patients with acne produce more sebum than do normal persons, although acne does not develop in all persons with high sebum levels.[30] It has also been demonstrated that the injection of whole sebum into the skin results in a pronounced lymphocytic inflammatory response and that sebum with the free fatty acids removed excites only a minimal inflammatory response.[41,44] In contrast, the injection into the skin of free fatty acids derived from sebum results in a decided inflammatory response similar to that caused by whole sebum, with rupture of pilosebaceous follicles and other histologic changes comparable with those occurring in acne.[44] This strongly suggests that the free fatty acids in sebum are largely responsible for the inflammatory reaction in acne. However, the presence of free fatty acids is not alone sufficient to produce inflammation in acne, since levels of free fatty acids in surface lipids are essentially the same in groups with and without acne.[16] Other factors as yet unelucidated appear to be necessary for free fatty acids to incite acne.

It is further known that there is little or no free fatty acid in lipids of intact sebaceous cysts[25] which suggests that the lipids of freshly secreted sebum must undergo hydrolysis during their passage through the follicular canal to the surface of the skin where sebum is found to contain up to 23 per cent free fatty acid.[19] Although there are several possible sources of such lipolytic activity, Scheimann and coworkers[36] have presented evidence that skin bacteria are a major source of such lipolytic activity.

Descriptions of the organisms comprising the cutaneous bacterial flora in acne have in part been somewhat conflicting; but two recent studies[37,38] have clearly demonstrated that two organisms constitute the overwhelming majority of the bacteria found in all forms of acne. Both are Gram-positive. One is an aerobe, *Staphylococcus albus,* and the other an anaerobic diptheroid, *Corynebacterium acnes.*

It has further been shown that injection of living *Corynebacterium acnes* into sterile steatocystomas (intact sebaceous cysts) results in rapid proliferation of the organism accompanied by the production of "products which irritated the lining, leading to leakage and rupture."[23] This in turn gives rise to a pronounced inflammatory reaction resembling an inflamed acne cyst. In view of the predominance of *Corynebacterium acnes* among the follicular bacteria and its probable role in the production of free fatty acids by hydrolysis of the esterified fatty acids of sebum in the follicle and on the surface, it seems reasonable to speculate that the "products" resulting from the injection of living *Corynebacterium acnes* into the sterile steatocystomas might well be free fatty acids.

Puhvel and coworkers[33] have shown that levels of antibody to *Cornyebacterium acnes* are elevated in the serum of patients with acne; whereas levels of antibody to *Staphylococcus albus*[34] are not; and this may reflect a direct involvement of *C. acnes* in the development of acne.

Accordingly, a reasonable working hypothesis might suggest that the inflammatory lesions of pustulocystic acne are due in part at least to the release of free fatty acids in the follicular ducts as a result of the lipolytic activity of *Corynebacterium acnes on sebum,* and that in susceptible persons these free fatty acids leak through the follicle wall, resulting in the clinical findings of pustules, cysts and inflammatory nodules.

Since *Corynebacterium acnes* is known to be highly sensitive to the broad spectrum antibiotics, including the tetracyclines,[29] a suitable test of this hypothesis would be to correlate the influence of the tetracyclines on the clinical course of acne with their influence on sebum free fatty acid levels. Just such a critical study was undertaken by Freinkel and coworkers,[16] and the results support the hypothesis noted above.

They found that administration of tetracycline orally to adult patients resulted in a qualitative alteration in the composition of sebum, the total quantity produced remaining unchanged. The change observed was a reduction in the concentration of free fatty acids, and it correlated well with amelioration of the inflammatory process and clinical improvement of the patient's acne. Although the study did not clearly demonstrate the basis for this activity of tetracyclines, the evidence previously cited strongly suggests that they act by reducing the number of *Corynebacterium acnes* organisms on the skin, and hence, their lipolytic activity.

The tetracyclines suppress *Corynebacterium acnes* on the skin as long as they are administered, but the organisms multiply rapidly after these agents are discontinued, usually reaching pretreatment levels within approximately two weeks.[18] Clinical relapse of patients with pustulocystic acne correlated well with rising values for free fatty acids in sebum ater discontinuation of tetracycline therapy,[16] further suggesting a relationship between the number of *Corynebacterium acnes* organisms, the amounts of free fatty acids and the clinical manifestations of acne.

Thus there is a rationale (developed, to be sure, long after the first clinical observations of its activity) to account for the efficacy of the tetracyclines in pustulocystic acne; and development of this rationale has illuminated and been illuminated by a better understanding of fundamental pilosebaceous pathophysiology.

Despite their effectiveness, the tetracyclines and other antibiotics should not, of course, be used in the routine management of all patients with acne, but should be reserved for the more severe, extensive and recalcitrant forms of the disease which do not yield to conventional therapy as alluded to above. In such patients, gratifying results may be observed within two to three weeks after the initiation of therapy and may be maintained as needed for months or even years, often with extremely low dosages. A typical regime consists of the use of a tetracycline in doses of 250 mg orally four times daily for the first one to three weeks until a positive result is obtained. This is followed by a gradual reduction of the dose to the lowest dose which is sufficient to maintain control of the acne. In some patients this may be as little as 250 mg every second or third day. In females who experience premenstrual exacerbations, uncontrolled with diuretics, an increase in the tetracycline dosage during the 10 to 14 days preceding the onset of menses to a level greater than the maintenance dose may bring about improved control.

Although the tetracyclines have been remarkably free of serious toxicity despite prolonged usage, a number of side effects are known to be associated with their use. Some of these side effects are trivial and do not ordinarily necessitate discontinuation of treatment. Others are grave and even life-threatening and represent absolute contraindications to tetracycline therapy for acne.

Among the serious complications are the development of severe and at times fatal liver damage in pregnant women given large doses of tetracycline in the presence of preexisting renal disease such as pyelonephritis.[51] The susceptibility of women to this complication may be further enhanced during the latter half of pregnancy because of a physiological decrease in clearance from the liver during this period.[8] Another problem associated with tetracycline therapy in the face of preexisting renal disease is the development of azotemia associated with decreased renal excretion of tetracycline, bringing about higher blood levels thus enhancing inhibition of protein synthesis and presenting the already damaged kidney with an increased nitrogenous load.

Another significant problem associated with long continued administration of tetracycline is discoloration of both temporary and permanent teeth.[47] This yellow-brown pigmentation may result from tetracycline administered from the fourth fetal month to the twelfth year of life.[24,53] Enamel hypoplasia has been noted in some, but not all, children with discoloration of the teeth due to tetracycline.[53] Reversible retardation of bone growth has also been observed in prematures receiving tetracycline.[7]

Thus it is apparent that tetracycline therapy is completely contraindicated for the management of acne in pregnant women and in children below the

age of 12 years, as well as in patients with preexisting renal or hepatic disease, especially in view of the usually long-term nature of such therapy.

Allergic reactions to tetracycline are rare[27] although anaphylactoid reactions have been reported.[13,15] With the exception of demethylchlortetracycline in which the incidence approaches 20 per cent,[5] photosensitization reactions are not common with tetracyclines.[5,6,26] Careful history coupled with clinical follow-up should avoid or promptly identify these side effects.

Nausea, vomiting, diarrhea and superinfection with bacteria and yeasts are all uncommon complications in otherwise healthy persons[27] and the debilitated patient who would be more susceptible to these problems is not likely to be a candidate for long-term tetracycline therapy for acne.

The incidence of intercurrent infections resistant to treatment appears to be no higher in acne patients treated with antibiotics for long periods than it is in comparable patients not so treated.[3,46]

Finally, since degraded tetracyclines may produce severe interference with renal tubular function, only "in date" drug which has not been subjected to extremes of heat and humidity should be used.[14,50]

Thus the tetracyclines have at present a secure place in the management of carefully selected patients with recalcitrant pustulocystic acne, but their use must be carefully supervised, and although at times it may seem convenient, refillable prescriptions should obviously not be dispensed.

Progestin-estrogen therapy

The androgen-stimulated increase in sebaceous gland activity occurring at puberty which provides the necessary but not sufficient basis for the development of acne vulgaris may be antagonized effectively by sufficient levels of estrogen. The precise mechanism of this activity is not established, but it is thought to be due to inhibition of ovarian androgen.[43] To exert this effect, doses well in excess of normal physiologic replacement amounts are required—at least 0.06 mg of ethynyl estradiol daily.[31] However, the pronounced menstrual abnormalities and menometrorrhagia resulting from employment of such doses has made estrogen alone an unsatisfactory therapeutic agent in many patients who might otherwise have benefited from such therapy. Because of feminization, estrogen therapy is, of course, not applicable to male patients.

The more recent development of a large series of progestin-estrogen combinations for contraceptive use has provided a group of compounds which have both the sebum suppressive effect desired for control of acne and good control of menstrual cycling.[42,43] There are a wide variety of such agents—one recent publication[35] lists over 70—but evidence indicates that their favorable effect in acne is due almost entirely if not entirely to the sebum-suppressive effect of the estrogenic moiety.[43] Quantitative sebum determinations demonstrate that clinical improvement and decrease in sebum levels are well correlated and that cyclic progestin-estrogen therapy for approximately two to five months is required to produce sebum suppression and clinical improvement in most women with acne,[43] the majority responding within the first three cycles.[28]

Such therapy should not be undertaken without adequate examination before it is begun, and careful observation during therapy is necessary.

An adequate pretherapy examination should include, at a minimum[17,35,48]

(1) History to rule out previous thromboembolic phenomena, thrombophlebitis, cerebrovascular accident, or estrogen dependent neoplasms;

(2) Physical examination including bimanual pelvic examination and speculum examination of cervix and vaginal vault to rule out malignant disease and fibroid tumors of the uterus (in young women with a virginal introitus, rectal examination is ordinarily preferred); breast examination to rule out carcinoma of the breast and, in the light of recent evidence,[48] routine ophthalmologic examination;

(3) Laboratory examination to include routine blood cell count, urinalysis, cytologic examination of cervical exudate, and a liver function test.

If results from these studies are within normal limits, selected women with recalcitrant pustulocystic acne unresponsive to the measures previously discussed may be considered for cyclic progestin-estrogen therapy of the older combined type or the more recent sequential type. Although there may be a flare of the acne during the first one or two cycles, control can ordinarily be expected within three to four cycles, occasionally five.[28,31,42,43] If no improvement is noted by the end of the fifth cycle, it is unlikely to occur with continued use of the compound although increased dose levels may achieve control.

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