Review Article

Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

THERAPY FOR ACNE VULGARIS

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ACNE vulgaris, or acne, as it is generally called, is the most common skin disease, affecting nearly 80 percent of persons at some time between the ages of 11 and 30 years.[1] It can persist for years and result in disfigurement and permanent scarring, and it can have serious adverse effects on psychosocial development, resulting in emotional problems, withdrawal from society, and depression.[2] The pathogenesis of acne is multifactorial, and therapy can now be directed at many of these factors. This review summarizes current concepts of the rational treatment of acne vulgaris.

PATHOPHYSIOLOGY OF ACNE

Acne vulgaris is the result of the obstruction of specialized follicles (sebaceous follicles),[3,4] which are located primarily on the face and trunk, by excessive amounts of sebum produced by sebaceous glands in the follicles combined with excessive numbers of desquamated epithelial cells from the walls of the follicles (Fig. 1).[5-8] The obstruction causes the formation of a microcomedo that may evolve into either a comedo or an inflammatory lesion. A resident anaerobic organism, *Propionibacterium acnes,* proliferates in the environment created by the mixture of excessive sebum and follicular cells[9,10] and produces chemotactic factors and proinflammatory mediators that may lead to inflammation.[11-16]

Acne begins in the prepubertal period, when the adrenal glands mature and secrete increasing amounts of adrenal androgens, which cause an increased production of sebum. With the development of the gonads, the production of androgens increases further, and the activity of the sebaceous glands increases. Most patients with acne probably have sebaceous glands that are hyperresponsive to androgens, rather than overproduction of androgens. However, acne frequently develops in patients with androgen excess.

The clinical expression of these pathophysiologic events ranges from noninflammatory open and closed comedones ("blackheads" and "whiteheads," respectively) to inflammatory papules, pustules, and nodules ("cysts"). Most patients have a mixture of noninflammatory and inflammatory lesions, although some have predominantly one or the other. It is not known why acne subsides in most patients but persists into adulthood or even throughout life in a few.

Therapies for acne exist that effectively counteract the excess production of sebum, the abnormal desquamation of epithelial cells in sebaceous follicles, and the proliferation of *P. acnes.* The choice of therapy for an individual patient depends on the extent, severity, and duration of the disease; the type of lesions; and the psychological effects of the disease.

THERAPIES FOR ACNE

Reduction of Sebum Production

No topical therapies influence the production of sebum. Soaps, detergents, and astringents can remove sebum from the surface of the skin but do not alter sebum production and are of no therapeutic value. In fact, vigorous scrubbing can aggravate acne by promoting the development of inflammatory lesions.[17] The use of abrasive cleansers and mechanical devices should be avoided for the same reason. "Blackheads" are not dirt to be rubbed off but are a result of interference in the transmission of light through compacted follicular cells. Gentle, nonabrasive cleansing is best.

Dietary factors, short of starvation, do not influence sebum production, and dietary restrictions have no role in therapy for acne. The sebum of patients with acne contains less linoleic acid than that of age-matched normal subjects. This deficiency may increase the desquamation of follicular epithelial cells in a manner similar to the way that systemic deficiency of linoleic acid increases the desquamation of the surface epithelium.[18]

Systemic drugs that influence sebum production include estrogens, antiandrogens such as cyproterone acetate (which is not available in the United States) and spironolactone, and the retinoid isotretinoin (Table 1). Sebaceous glands are androgen-dependent, and therefore it is not surprising that estrogens and antiandrogens are useful in therapy. In the case of estrogens, which are usually prescribed as a combined estrogen–progestin contraceptive, the beneficial effects are most apparent at doses of 50 μg or more of

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ethinyl estradiol (or equivalent doses of other estrogens).[19,20] Modern oral contraceptives contain 35 μg or less of ethinyl estradiol and are not as effective in suppressing sebum production. Nevertheless, a low-dose oral contraceptive, particularly one that contains a nonandrogenic progestin such as norgestimate or desogestrel, can be effective. The contraceptive must be given for two to four months before any improvement occurs, and relapses may occur if treatment is discontinued. In general, prolonged therapy, often for years, is needed to control acne.

In sebaceous glands, testosterone is converted to the more active dihydrotestosterone by 5α-reductase. Drugs that inhibit type II reductase are available but have not yet been shown to be effective in reducing sebum production, suggesting that the type I isoenzyme may be the active form in sebaceous glands. Cyproterone acetate is a potent antiandrogen that is effective in both high and low doses.[21-24] It is widely used in Europe but is not available in the United States. Spironolactone in doses of 100 to 200 mg per day reduces sebum production and improves acne, and it may be effective in doses as low as 25 to 50 mg per day.[25,26] As with estrogen therapy, several months of spironolactone therapy are required before the maximal benefit occurs, and prolonged therapy is needed to maintain improvement. Only women should be treated with antiandrogens, and because of the potential feminizing effects on a male fetus, women undergoing treatment should practice effective birth control.

Isotretinoin (13-*cis*-retinoic acid), a natural metabolite of vitamin A, when given in pharmacologic doses profoundly reduces sebum production and results in prolonged remissions of even the most severe forms of acne.[27] A four-to-five-month course of therapy with daily oral doses ranging from 0.1 to 1.0 mg per kilogram of body weight results in remission in nearly all patients. Remission lasts longer in patients treated with higher doses[28,29] and can be permanent. The results of one study suggested that the total cumulative dose may determine the duration of remission, with the best results observed in patients who received a total of 120 mg per kilogram.[30] Long-term follow-up studies indicate that

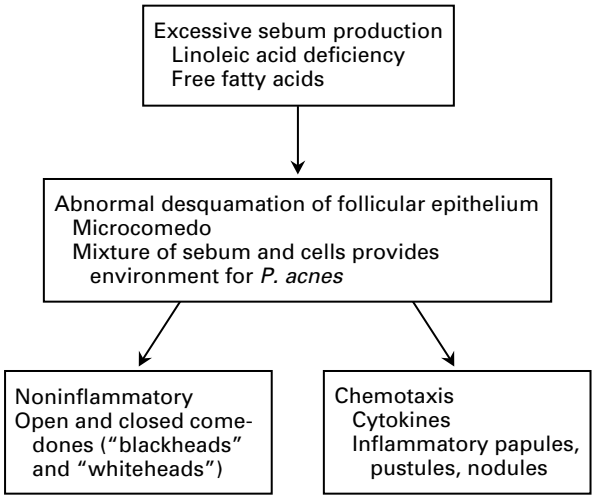


Figure 1. Pathophysiology of Acne.

TABLE 1. MAJOR PATHOPHYSIOLOGIC FEATURES OF ACNE AND DRUGS THAT AFFECT THEM.

FEATURE	SYSTEMIC DRUGS	TOPICAL DRUGS
Sebum overproduction		None
Only systemic agents work; use only in most severe cases	Estrogens Antiandrogens Spironolactone Isotretinoin	
Abnormal desquamation of follicular epithelium		
Present in all patients	Isotretinoin Antibiotics (indirect effect)	Tretinoin (most effective) Salicylic acid Adapalene Tazarotene Isotretinoin Antibiotics (indirect effect)
P. acnes proliferation		
Present in all patients with inflammatory lesions; extent and severity determine whether to use topical or systemic therapy	Tetracycline Erythromycin Minocycline Doxycycline Trimethoprim–sulfamethoxazole Clindamycin Isotretinoin (indirect effect)	Erythromycin Clindamycin Benzoyl peroxide Benzoyl peroxide plus erythromycin Azelaic acid Benzoyl peroxide plus glycolic acid
Inflammation	Corticosteroids Isotretinoin	Metronidazole Intralesional corticosteroids

TABLE 2. TOPICAL AND SYSTEMIC ANTIBIOTICS USED TO TREAT ACNE.

ANTIBIOTIC	CHARACTERISTICS
Topical	
Benzoyl peroxide	Lipophilic, may cause irritation; contact allergy in up to 1% of patients
Erythromycin	*P. acnes* very sensitive; least lipophilic
Clindamycin	*P. acnes* very sensitive; more lipophilic than erythromycin, but less than benzoyl peroxide
Benzoyl peroxide plus erythromycin	*P. acnes* very sensitive; most lipophilic topical agent; less irritating than benzoyl peroxide alone
Azelaic acid	*P. acnes* sensitive; minimal lipophilia; can reduce abnormal desquamation
Metronidazole	*P. acnes* not sensitive; has antiinflammatory properties
Benzoyl peroxide plus glycolic acid	Glycolic acid may enhance penetration and reduce abnormal desquamation
Systemic	
Tetracycline	*P. acnes* sensitive; inexpensive; usually needs to be taken two to four times a day; compliance can be a problem because of need to take on an empty stomach
Erythromycin	*P. acnes* very sensitive; resistance beginning to emerge; gastrointestinal upset common; inexpensive
Doxycycline	Lipophilic; *P. acnes* very sensitive; resistance not yet a problem; photosensitivity can occur; more expensive than tetracycline and erythromycin
Minocycline	Lipophilic; *P. acnes* very sensitive; resistance not yet a problem; no photosensitivity; abnormal pigmentation in oral mucosa and skin; vertigo-like symptoms can occur; most expensive
Trimethoprim–sulfamethoxazole	Lipophilic; *P. acnes* very sensitive; severe erythema multiforme and toxic epidermal necrolysis limit use
Clindamycin	*P. acnes* very sensitive; somewhat lipophilic; pseudomembranous colitis limits use

approximately 60 percent of patients remain free of acne after a single course of therapy.[30,31]

Isotretinoin would be the drug of choice for most patients with acne if it did not have so many side effects. These include arthralgia, stiffness and tendinitis, and elevated serum lipid concentrations. Most important, isotretinoin is teratogenic.[31] Any woman for whom treatment with isotretinoin is planned must be proved not to be pregnant when treatment is begun and must understand the need for effective contraception during therapy and for at least one month after it is discontinued (the drug is not stored in any tissue).

Reduction of Epithelial Desquamation in Sebaceous Follicles

Excessive desquamation of follicular epithelium in sebaceous follicles, in conjunction with excessive production of sebum, results in the formation of microcomedones (comedogenesis), which may evolve into noninflammatory open and closed comedones or into inflammatory lesions if *P. acnes* proliferates and proinflammatory mediators are produced (Fig. 1).[5,6] Three topical agents that affect the desquamation of follicular epithelial cells are currently available: tretinoin, isotretinoin, and salicylic acid. Newer retinoids, such as tazarotene, and new formulations of tretinoin are expected to receive approval soon from the Food and Drug Administration (FDA) (Table 1). A recently approved antimicrobial agent, azelaic acid, has also been reported to have some activity against comedogenesis.

Topical tretinoin (all-*trans*-retinoic acid) slows the desquamation process, thereby reducing the numbers of both microcomedones and comedones.[32] Topical isotretinoin has a similar effect[33] and is available in many countries, but not yet in the United States. Tretinoin is available in several concentrations as both cream (0.025, 0.05, and 0.1 percent) and gel (0.01 and 0.025 percent); these different formulations allow the therapy to be adjusted to the sensitivity of the patient's skin and to the climate. For example, gels are preferred in hot and humid climates and creams in cold and dry climates. Tretinoin and isotretinoin are commonly used in combination with either topical or systemic antibiotics,[34,35] thus directing therapy against two of the major causes of acne.

Antibiotics appear to exert an indirect effect on comedogenesis. In clinical trials with topical or systemic antibiotics, there was a small (20 percent) but consistent reduction in the number of noninflammatory comedones, as compared with a 60 percent reduction with tretinoin.[32] This effect suggests that *P. acnes* generates comedogenic materials, with free fatty acids being the most likely candidates.

Salicylic acid is available over the counter in 0.5 and 2 percent hydroalcoholic formulations. This

drug has a weaker effect on comedogenesis than tretinoin or isotretinoin but is nevertheless useful.[36]

Systemic isotretinoin exerts a primary effect on comedogenesis, causing both a decrease in the size of comedones and a reduction in the formation of new ones.[37]

Prevention of Proliferation of *P. acnes*

P. acnes is usually found in low numbers on normal skin. The mixture of abnormally desquamated cells and excessive amounts of sebum in microcomedones produces an environment that favors the growth of *P. acnes. P. acnes* produces proinflammatory mediators that cause the formation of inflammatory lesions. *P. acnes* is highly sensitive in vitro to many antibiotics, but not many of them can gain access to the lipid-rich environment of the sebaceous follicles where the organism is proliferating.

Choices for topical therapy include formulations of erythromycin, clindamycin, metronidazole, azelaic acid, benzoyl peroxide, and the combination of benzoyl peroxide and erythromycin or glycolic acid (Table 2). When applied once or twice daily, these drugs exert a beneficial effect both by killing *P. acnes* and by inhibiting the production of proinflammatory mediators by organisms that are not killed.[38,39]

Benzoyl peroxide is available in 1, 2.5, 5, and 10 percent solutions in gel and lotion formulations. It is lipophilic and suppresses the growth of *P. acnes* more effectively than topical antibiotic formulations of clindamycin and erythromycin other than the combination of benzoyl peroxide and erythromycin.[40] It has no intrinsic antiinflammatory properties, and it causes local irritation and allergic contact dermatitis more often than topical antibiotics. Benzoyl peroxide is also available as a 5 percent solution in combination with 3 percent erythromycin and as a 7 percent solution in combination with glycolic acid.

Topical clindamycin reduces *P. acnes* more effectively than topical erythromycin in vivo, but clinical trials indicate that their efficacy is similar.[40] Topical azelaic acid has been shown to reduce *P. acnes* to about the same degree as topical clindamycin.[41] The combination of benzoyl peroxide and erythromycin, however, is probably the most effective topical antibiotic therapy against *P. acnes.*[41]

The choices for systemic antibiotic therapy include tetracycline, erythromycin, minocycline, doxycycline, clindamycin, and trimethoprim–sulfamethoxazole.[42] Doxycycline, minocycline, and trimethoprim–sulfamethoxazole are more lipid-soluble than tetracycline and erythromycin, and they are generally considered to be more effective and less potent than the latter two drugs. The usual daily doses are 500 to 1000 mg of tetracycline or erythromycin and 50 to 200 mg of doxycycline or minocycline. Absorption of the latter two drugs is not reduced by dairy products and food to the same degree as that of tetracycline.[43] When the development of new inflammatory lesions has ceased, which usually occurs in four to six weeks, the dose of antibiotic may be slowly tapered. Relatively uncommon but important side effects of minocycline include allergic urticarial reactions, vertigo-like symptoms, and deposition of a carbofuscin-like pigment in the skin. All the tetracyclines can stain developing teeth and should not be used in children until the permanent teeth are in place. Doxycycline can induce photosensitivity reactions. Erythromycin causes gastrointestinal upset in many patients but is much cheaper than minocycline or doxycycline, as is tetracycline.

P. acnes is very sensitive to cephalosporins in vitro. However, it is not known whether cephalosporins penetrate sufficiently into sebaceous follicles to reduce *P. acnes.* Penicillin and closely related derivatives are not effective against *P. acnes.*[44]

Most patients require prolonged courses or frequent intermittent courses of antibiotic therapy before permanent remission occurs. Fortunately, *P. acnes* is highly sensitive to many antibiotics, and the development of resistance is uncommon.[45] However, strains of *P. acnes* that are less sensitive to antibiotics have recently become more prevalent.[46,47] The clinical importance of the reduced sensitivity is not known, although concern about the future of antibiotic therapy has been voiced.[47] In most patients, the less sensitive strains of *P. acnes* make up only a small portion of the total population of *P. acnes.*

THERAPEUTIC DECISIONS

The treatment of acne starts with the recognition that it is a disease that can have profoundly adverse psychosocial effects and that therapy is warranted. Physicians should dispel the myth that diet or failure to cleanse the skin is responsible for acne. Therapy should be directed against the several causes of acne (Table 1).

In most patients, a combination of drugs aimed at correcting abnormal desquamation and reducing the proliferation of *P. acnes* is sufficient to control acne. For more severely affected patients with no response to this approach, therapy to suppress sebum production is indicated.

Comedonal Acne

The earliest clinical expression of acne is usually noninflammatory comedones, which are typically found on the central forehead, chin, nose, and paranasal areas (Fig. 2A). This form of acne develops in the pre-teenage or early teenage years and is a consequence of increased sebum production and abnormal desquamation of epithelial cells. Colonization with *P. acnes* has not yet occurred, and therefore there are no inflammatory lesions. The main thrust of therapy is preventive, to minimize the formation of new comedones and the production of an environment favorable to the proliferation of *P. acnes.*

Topical tretinoin or adapalene is the treatment of choice, with salicylic acid as the alternative. Topical tretinoin should be applied once daily, starting with a lower concentration of the cream (available in 0.025, 0.05, and 0.1 percent concentrations) or gel (available in 0.01 and 0.025 percent concentrations) and increasing the concentration if local irritation does not occur. Adapalene, a naphthoic acid with retinoid activity, has recently been approved at a concentration of 0.1 percent in a gel derivative by the FDA. Topical adapalene has clinical benefits similar to those of topical tretinoin and causes less local irritation.[48,49] Topical azelaic acid has some comedolytic activity. It is less potent than tretinoin but may be useful in patients who cannot tolerate topical tretinoin or other retinoids.[41] Newer formulations of tretinoin that may be less irritating are under review by the FDA. Patients should be told that several months of therapy will be needed to achieve an optimal response and that treatment should be continued until it is clear that new lesions are not developing.

Mild Inflammatory Acne

In many early-teenage patients, after an initial phase of noninflammatory comedonal acne, a mild form of inflammatory acne develops in which there are scattered small papules or pustules with a minimum of comedones (Fig. 2B). This type of mild inflammatory acne also tends to develop in adult women in their 20s. These lesions arise from microcomedones in which there is both abnormal desquamation of follicular epithelium and proliferation of *P. acnes*. Most patients have a response after two to four weeks of twice-daily application of a topical antibiotic, topical benzoyl peroxide, or the combination of benzoyl peroxide and erythromycin. Treatment should be continued until no new lesions develop and then should be slowly discontinued. Numerous topical antibiotics are available (Table 2).

Inflammatory Acne

Most patients with acne present with comedones, papules, and pustules on the face and trunk (Fig. 2C). The earlier stages of noninflammatory comedonal acne, followed by small numbers of inflammatory lesions on the face, typically evolve into a more generalized eruption, first on the face and then on the trunk. A few patients later have a more destructive type of inflammation associated with large, deep inflammatory nodules (often referred to as cysts) (Fig. 2D).

The goal of therapy for these patients is to neutralize the pathophysiologic events. In patients with comedones and papulopustular lesions, the combination of a topical retinoid applied once daily and either a topical or a systemic antibiotic is the best approach (Table 2). The choice between topical and systemic antibiotic therapy usually depends on the extent of skin involvement and the severity of the inflammation. Benzoyl peroxide and benzoyl peroxide plus erythromycin are the most effective topical antimicrobial therapies. Topical clindamycin and erythromycin are also effective and are widely used. Usually four to six weeks are needed to reduce *P. acnes* and to curtail the formation of new inflammatory lesions. Patients treated with an oral antibiotic may also be given topical antibiotics, particularly when the dose of the oral drug is reduced. In general, the dose of an antibiotic should not be reduced before two to four months. Long-term control requires the suppression of *P. acnes* for prolonged periods. For patients with larger inflammatory lesions, local injection of a corticosteroid is effective in suppressing acute inflammation.

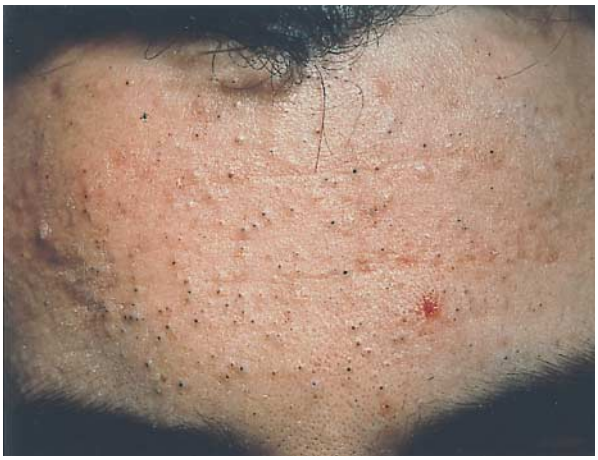
Patients with widespread nodular cystic lesions may respond to oral antibiotic therapy, but the response is usually incomplete. In these patients, particularly those who have scarring, systemic isotretinoin is the treatment of choice. Although this drug has revolutionized the treatment of severe acne, it needs to be used with care because of its side effects. A four-to-five-month course of 0.1 to 1.0 mg per kilogram per day causes complete remission in nearly all patients. In a few patients, the acne worsens initially, and concomitant systemic corticosteroid therapy may be needed.

An alternative to systemic isotretinoin in women with persistent acne that is unresponsive to therapy with antibiotics and topical tretinoin is therapy with estrogen or an antiandrogen. Women with very irregular menses or those with hirsutism should be evaluated gynecologically as well as hormonally. Those with excessive adrenal androgen production should receive systemic corticosteroid therapy, and those with excessive ovarian androgen production should receive an oral contraceptive. The latter is often effective in women with normal menses and no signs of excess androgen production.

In an uncommon variant of inflammatory acne, there is an acute transformation from typical inflammatory acne to highly destructive inflammation, usually associated with fever, leukocytosis, arthralgia, inflammatory bone lesions, and transient glomerulonephritis (Fig. 2E).[50-53] This variant is referred to as acne fulminans because of its abrupt onset and the destructive inflammation. Oral corticosteroids are the therapy of choice.

Another acute, highly inflammatory type of acne is often referred to as pyoderma faciale because of the acute appearance of numerous large pustules and furunculoid nodules.[53,54] Most patients are women who have received androgen therapy or have undergone severe emotional stress. Oral isotretinoin is the treatment of choice.

The most common form of intense inflammation is acne conglobata. It is characterized by large numbers of deep, inflammatory nodules, some of which coalesce and form undermining epithelial sinus tracks on the face and trunk; it commonly heals with scar-



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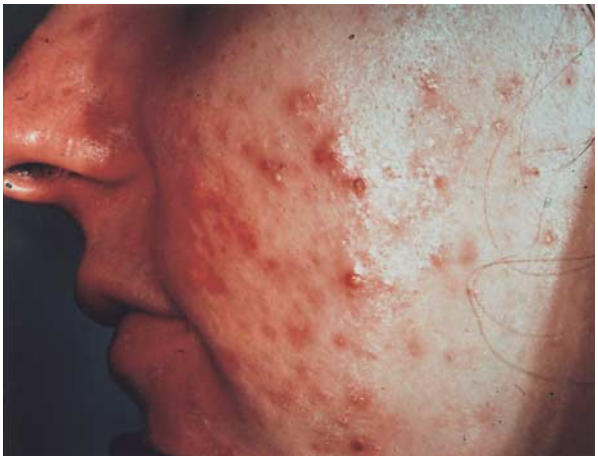

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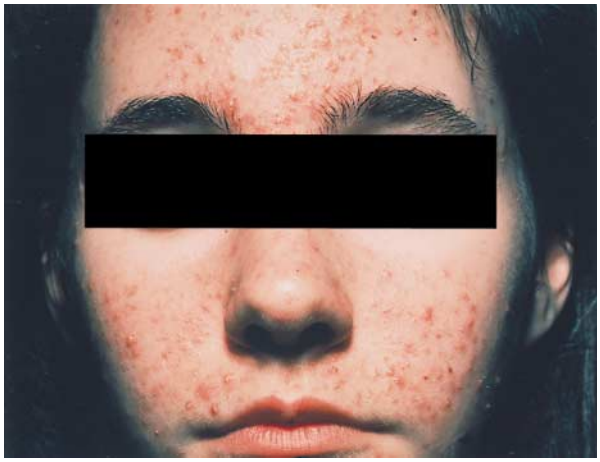

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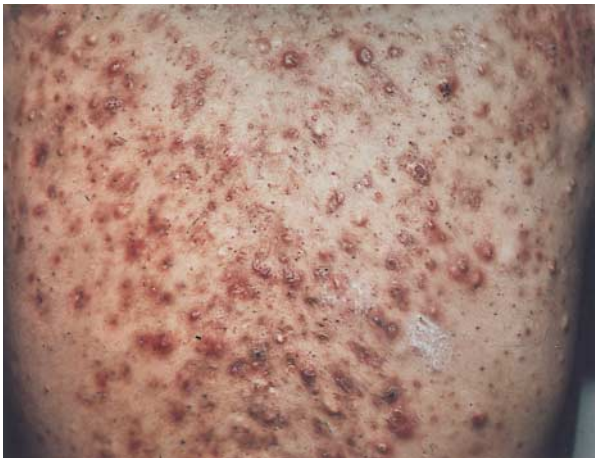

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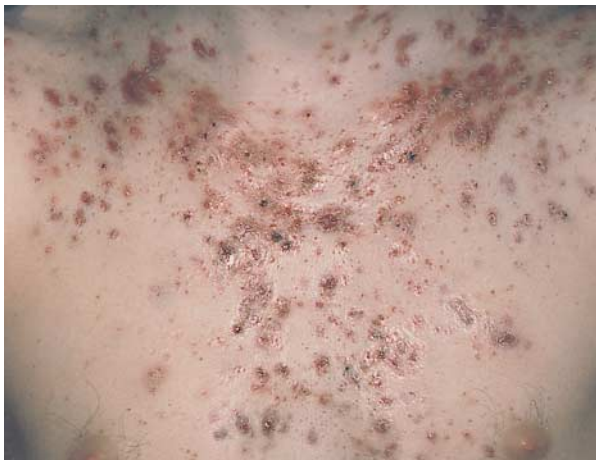

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Figure 2. Photographs of Patients with Acne.

Panel A shows noninflammatory comedonal acne ("blackheads" and "whiteheads") on the forehead. Topical therapy with a retinoid alone is usually sufficient; salicylic acid is the second choice. Panel B shows papular inflammatory acne. Therapy with a topical antibiotic alone is usually effective. Panel C shows widespread comedones and inflammatory lesions developing over most of the face. A systemic antibiotic in combination with a topical retinoid is the most effective therapy. Panel D shows severe nodular and cystic acne of the trunk. Topical or systemic antibiotic therapy is usually ineffective, and systemic isotretinoin is the treatment of choice. Panel E shows explosive inflammatory acne of the chest associated with ulcerative lesions, fever, leukocytosis, and arthralgia; this variant is known as acne fulminans. Systemic corticosteroid therapy is required.

ring. Oral isotretinoin is the treatment of choice in patients with this type of acne; in some, systemic corticosteroid therapy may be given before or concomitantly with isotretinoin.

CONCLUSIONS

New information about the pathophysiology of acne has led to the development of drugs that are effective in most patients, so that there is now no reason for patients to wait for spontaneous remission and to endure physical and emotional scarring. Treatment with combinations of topical or systemic drugs results in the control of all forms of this disease, even the most inflammatory and destructive variants.

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