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# Manual of Dermatologic Therapeutics

Sixth Edition

配英汉索引

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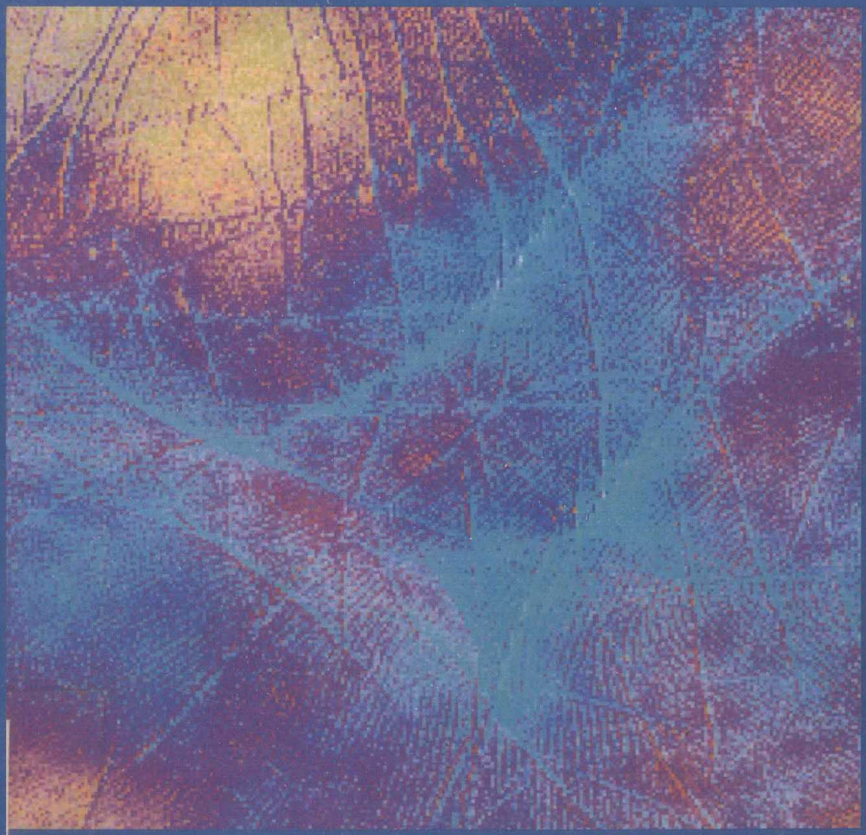

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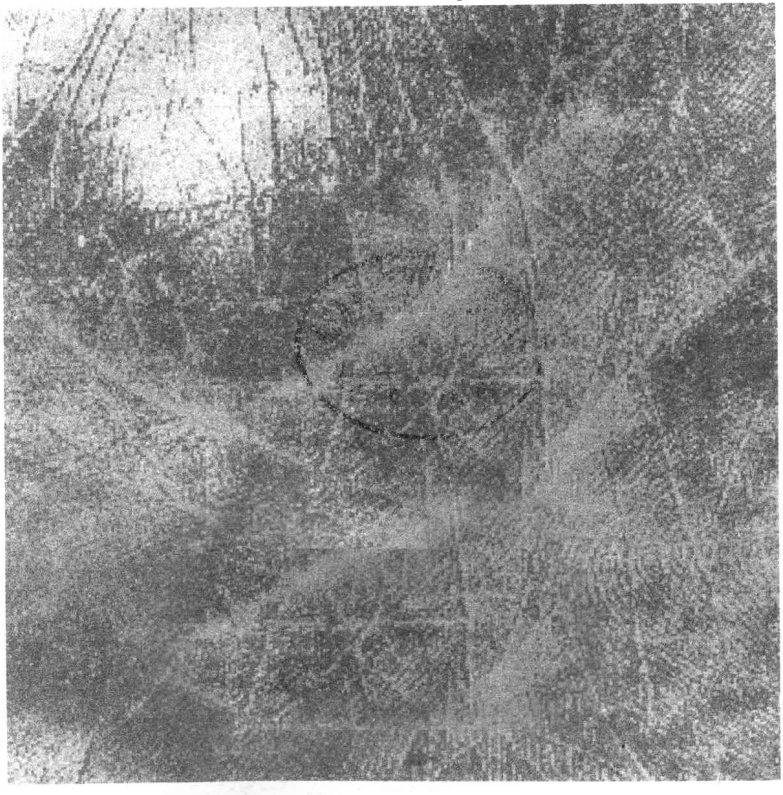

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# Manual of Dermatologic Therapeutics
## With Essentials of Diagnosis

Sixth Edition

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To my family, with love: Anne, David, Jennifer, Pablo, and Alexander.

*KAA*

To my mother and father.

*KEB*

# PREFACE

The material in this manual was originally prepared in a less detailed form for use by physicians, nurses, and other health care personnel at the Harvard Community Health Plan. The reception given such practical therapeutic guidelines by clinicians of various specialties, by medical students at the Harvard Medical School, and by house officers at the Harvard teaching hospitals encouraged expansion to a more comprehensive work.

The first five editions of *Manual of Dermatologic Therapeutics* have been greeted enthusiastically. It is gratifying that such an approach to rational therapeutics has become widely adopted and that this information has been further disseminated through Spanish, Portuguese, French, Italian, Indonesian, Japanese, and Taiwanese editions.

The sixth edition has been significantly revised and rewritten in collaboration with Drs. Murad Alam, Rachel Reynolds, and Sandy Tsao. New and updated textual, reference, and illustrative material has been added.

The *Manual* presents up-to-date information on the pathophysiology, diagnosis, and therapy of common cutaneous disorders. Diagnostic procedures and surgical and photobiologic techniques are explained in both theoretical and practical terms. The pharmacology, structure, and optimal use of dermatologic medication are discussed in detail.

The first portion of the *Manual* is organized so that a disease is defined initially and its pathophysiology is discussed according to the problem-oriented record system. Each disease is then subdivided into subjective data (symptoms), objective data (clinical findings), assessment, and therapy sections. A sequence of therapeutic interventions and alternative approaches to treatment is emphasized. The remainder of the text is concerned with procedures, techniques, treatment principles, and discussion of the pharmacodynamics and usage of specific medications employed in treating cutaneous disease.

We hope that the sixth edition of the *Manual* is as helpful an educational and practical guide to therapeutics and disease management as have been the previous five.

*Kenneth A. Arndt, M.D.*
*Kathryn E. Bowers, M.D.*

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# 1. ACNE

I. **Definition and pathophysiology.** Acne, a very common, self-limited, multifactorial disorder involving the sebaceous follicles, is usually first noted in the teenage years. Lesions may begin as early as ages 8 to 10 years at *sebarche,* which in girls may precede menarche by more than a year. Prevalence increases steadily throughout adolescence *and then decreases in adulthood.* Though girls often develop acne at a younger age than boys, severe disease affects boys 10 times more frequently (up to 15% are involved). Patients with severe cystic acne often have a positive family history of the same.

Neonatal acne or cephalic pustulosis is self-limited and occurs during the first 2 weeks of life. Almost one in five newborns are affected by at least mild neonatal acne characterized by erythematous non-scarring papules on the face and neck. This disorder self-resolves in 1 to 3 months. Infantile acne (usually at age 3 to 6 months) includes persistent comedones and inflammatory lesions with an increased risk of scarring. Boys are more often affected than girls due to high testosterone levels from age 6 to 12 months. Individuals with infantile acne may have more severe teenage acne than their peers. One study implicated Malassezia organisms in infantile acne, and patients do respond to the imidazole creams. Some of these infants may eventually require isotretinoin (Accutane). Acne in midchildhood may be a marker for adrenal or gonadal tumors.

A significant increase in adult acne has been observed over the last several decades. A recent study by Goulden found the prevalence of acne in a group aged 25 to 58 years to be 3% of men and 12% of women. Eighty-two percent of the individuals had experienced acne since teenage years and most did not see a decrease until after age 45. In another study by Goulden, 50% of patients with adult acne had a first-degree relative with post adolescent acne; one-third of the women had at least one symptom of hyperandrogenism and 37% of the entire group had failed a course of Accutane (1).

The principal factors involved in the pathogenesis of acne are increased sebum production, abnormal keratinization of the follicular epithelium, proliferation of *Propionibacterium acnes,* and inflammation. Severity of involvement often corresponds to the amount of sebum secreted; patients with severe acne usually will have large and active sebaceous glands with prominent follicular openings ("pores") and oily skin ("seborrhea"). However, there is much variation and overlap in sebum secretion between unaffected control subjects and acne patients, and no evidence has yet been found that sebum in acne patients differs qualitatively from that in normal persons.

Androgens are the only stimulus to sebaceous gland development and secretion. Lucky observed that adrenal maturation alone, with elevated dehydroepiandrosterone sulfate (DHEAS) levels, may be sufficient stimulus for sebum production in patients prone to cystic acne (1a). Early comedonal acne development is highly predictive of later, more severe disease. Early onset acne may be the first sign of an underlying hormonal abnormality, especially if there is an associated advanced bone age and early pubic hair development.

At puberty, hormonal stimuli lead to increased growth and development of sebaceous follicles. Female patients with severe acne or evidence of virilization often have abnormally high levels of circulating androgens. Several recent studies have demonstrated that many female patients with milder forms of acne and no evidence of virilization may still have ovarian and/or adrenal overproduction of androgens. In those patients with normal circulating levels of androgens, there is some evidence that suggests a heightened end-organ responsiveness of the sebaceous glands to androgenic stimulation. This heightened end-organ response results in increased conversion of testosterone to dihydrotestosterone (DHT) and other 5 alpha-reduced metabolites or suppressed follicular testosterone metabolism. Male acne patients tend to have higher levels of androstenedione, testosterone, free androgen index, and 11-deoxycortisol (2).

The enlarged gland secretes sebum into a dilated follicle that contains a disproportionately large quantity of normal cutaneous bacteria. Sebum contains free and esterified fatty acids as well as unsaponifiable lipid components. It is the free fatty acid (FFA) fraction of sebum, produced in the sebaceous follicle by the action of enzymes associated with the anaerobic diphtheroid *P. acnes* that acts as the primary irritating substance in inflammatory acne. As triglyceride levels rise, so does the population of *P. acnes*. In addition, *P. acnes* produces low-molecular-weight peptides, which act as chemoattractants for polymorphonuclear leukocytes. Patients with severe acne demonstrate cell-mediated immunity directed toward *P. acnes*, the severity of inflammation is proportional to the anti-*P. acnes* immunity. Other evidence for immune mechanisms includes the observation of complement component C3 in the walls of dermal blood vessels and the basement membrane zone of acne lesions. Attraction and killing of leukocytes by comedonal components, the resultant inflammatory cascade, and specific immunologic events probably all contribute to the final appearance of an inflammatory acne lesion.

Disordered shedding of the cells that line sebaceous follicles is another factor in the pathogenesis of acne lesions. Large numbers of desquamating horny cells tend to stick together rather than flow to the surface with sebum. Experimentally, follicular hyperkeratosis is induced by Interleukin 1 alpha (IL-1 alpha) and epidermal growth factors and isotretinoin inhibits this process. The resulting impacted lipid and keratin mass expands to fill the lumen and forms a solid plug in the dilated opening, becoming a closed comedo ("whitehead"). If this comedonal mass protrudes from the follicle, it is recognized as an open comedo ("blackhead"). Whether its dark color is due to oxidized lipid, melanin, or densely packed keratinocytes and bacteria, this plug most assuredly is *not* dirt. As hydrolytic enzymes released from polymorphonuclear leukocytes induce follicle walls to leak or rupture, sebum (with its irritant and chemoattractant factors), keratin, bacteria, and hair are released into the dermis and result in an inflammatory mass (papule, "pimple," pustule, nodule, cyst, and/or abscess).

Activation of the classic and alternative pathways of complement by *P. acnes* enhances the inflammation. Most acne papules or pustules result from rupture of an intrafollicular microcomedo rather than a visible one. Patients with large numbers of comedones usually have only small numbers of inflammatory lesions, whereas patients with severe cystic acne usually have few comedones. In adult life, the cells lining the follicle presumably become less susceptible to comedogenic materials. Spontaneous disappearance of acne also may be related to a decreased dermal reactivity to irritant substances.

As many as one-third of adult women are affected by a low-grade acneform eruption that may start *de novo* or merge imperceptibly with preexisting adolescent acne. The eruption may be induced by chronic exposure to comedogenic substances such as isopropyl myristate, cocoa butter, and fatty acids present in some creams and moisturizers, by androgenic stimuli from progestins present in some oral contraceptives, by recent cessation of oral contraceptives, or by unknown causes.

Acne may lead to pitted or hypertrophic scarring. If left alone, most inflammatory acne tends to disappear slowly in the early twenties in men and somewhat later in women. Adequate therapy will in all cases decrease its severity and may entirely suppress this disease. The link between acne and rosacea is unknown; some adult patients may have features of both diseases as their acne is decreasing and signs and symptoms of rosacea are increasing.

II. **Subjective data**

A. Patients' complaints may be related to inconspicuous lesions that nevertheless cause considerable social embarrassment. As with all medical and psychological conditions, the patient's perception of the severity of the problem is an important guide to treatment, and judgmental decisions by the physician about the severity of objective disease must be evaluated in this context.

A quality of life scale has been developed specifically for the acne patient. Respondents answer on a grade of 0 to 3 to what extent they have experienced each item.

1. Feeling self-conscious in the presence of others.
2. Decrease in your socialization with others.

3. Difficulties in your relationships with your spouse or partner.
4. Difficulties in your relationships with your close friends.
5. Difficulties in your relationships with your immediate family.
6. Feeling like an "outcast" most of the time because of the effect of acne upon your appearance.
7. People making fun of your appearance.
8. Feeling rejected in a romantic relationship because of the effect of acne upon your appearance.
9. Feeling rejected by your friends because of the effect of acne upon your appearance.

B. Inflammatory lesions of acne may itch as they erupt and may be very painful on pressure.
C. Pustules and cysts often rupture spontaneously and drain a purulent and/or bloody but odorless discharge.

III. **Objective data (See color insert.)**
A. **Noninflammatory lesions.** The initial lesion is the closed comedo; visible as a 1 to 2-mm white dot (whitehead) most easily seen when the skin is stretched. If follicle contents extrude, a 2 to 5-mm, dark-topped, open comedo (blackhead) results.
B. **Inflammatory lesions.** Erythematous papules, pustules, cysts, and abscesses may be seen. Patients with cystic acne also tend to show "double," or polyporous, comedones, which result from prior inflammation during which epithelial tongues have caused fistulous links between neighboring sebaceous units. Acne lesions are seen primarily on the face, but the neck, chest, shoulders, and back may be involved. One or more anatomic areas may be involved in any given patient, and the pattern of involvement, once present, tends to remain constant.
C. The skin, scalp, and hair are frequently very oily.

IV. **Assessment.** Several points regarding etiology or therapy should be considered with each patient:
A. Are endocrine factors important in this patient? Sudden onset of acne, treatment-resistant acne, and acne associated with signs of androgenism *should lead one to suspect an endocrine abnormality.*
1. Are menstrual periods regular? Is there any hirsutism? (Stein–Leventhal syndrome, Cushing's syndrome, 21-hydroxylase deficiency, and other endocrinopathies are frequently accompanied by acne.) As many as 80% of women with acne may have polycystic ovaries. This disorder is defined by menstrual irregularities, acne, pelvic ultrasound imaging of subcapsular ovarian cysts, and an elevated luteinizing hormone (LH) to follicle stimulating hormone (FSH) ratio (a level greater than 2 to 3 is suggestive). The testosterone elevations are modest in the range of 80 ng/dl to 150 ng/dl.

Men and women with mild to severe cystic acne, especially those who do not respond to conventional therapy, may have elevated plasma-free testosterone and/or DHEAS levels. Hyperandrogenism is associated with acne, hirsutism, alopecia, and menstrual irregularities; other possible findings include infertility, deepening of the voice, increased libido, acanthosis nigricans, insulin resistance, type 2 diabetes, mellitus and dyslipidemia. DHEAS elevations above 8,000 ng/ml suggest the presence of an adrenal tumor; a range of 4,000 ng/ml to 8,000 ng/ml is indicative of congenital adrenal hyperplasia. Testosterone elevations point to an ovarian dysfunction, with levels of 150 nd/dl to 200 nd/dl suggesting an ovarian tumor. Oral contraceptives can mask an underlying endocrine disorder, so testing should be done 1 month after discontinuation of the hormones. Women may have high normal levels of DHEAS and testosterone and may benefit from hormonal therapy. Postmenopausal acne occurs in dark-complexioned women with previously oily skin, with the development of small closed comedones at the periphery of the face; unopposed adrenal androgens are the presumed cause.