Manual of Dermatologic Therapeutics

With Essentials of Diagnosis

Third Edition

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Preface

The textual 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 several of the Harvard teaching hospitals encouraged me to write this more comprehensive work.

The first and second editions of the *Manual of Dermatologic Therapeutics* have been greeted enthusiastically. It is gratifying to realize that such an approach to rational therapeutics has become widely used in the United States, and to know that the information will find good use throughout the world through the Spanish, Portuguese, Italian, Indonesian, and Taiwanese editions.

The third edition has been significantly revised and rewritten, and much new material has been added. It continues to be surprising how so much changes in so short a time, especially in regard to the pathophysiology and approach to the treatment of cutaneous disease.

The *Manual* presents up-to-date information on the pathophysiology, diagnosis, and therapy of common cutaneous disorders. Dermatologic diagnostic procedures and surgical and photobiologic techniques are explained in both theoretical and practical terms. The pharmacology, structure, and optimal use of dermatologic and selected systemic medications are included along with current costs for both trade and generic drugs. Information in greater depth about some subjects may be found in several excellent comprehensive works.* Entities that require specialized therapy, such as malignant tumors of the skin, and conditions seen primarily in the hospital patient have been purposely omitted.

The first portion of the *Manual* is organized so that each entity is initially defined and its pathophysiologic features are discussed; each disease is then subdivided into subjective data (symptoms), objective data (clinical findings), assessment, and therapy sections, according to the problem-oriented record system in use in many institutions throughout the country. The rest 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.

I would like to express my appreciation to several colleagues across the country for their review of the material. Drs. Arthur Z. Eisen, John H. Epstein, David S. Feingold, Thomas B. Fitzpatrick, Irwin M. Freedberg, and Silas E. O'Quinn all offered constructive criticism on the first edition. Dr. Barbara A. Gilchrest reviewed the second edition. Dr. Jeffrey Bernhard carefully read the third edition and made numerous helpful suggestions about both syntax and content. He is also responsible for the first draft and much of the material in the sections on The Principles of Normal Skin Care and the Use of Systemic Steroids in Dermatology. Jeffrey P. Ross, B.S., R.Ph., offered valuable advice about current pharmaceutical pricing and pharmacy practices. My thanks go to the Schering Corporation, Kenilworth, New Jersey, 07033 for permission to reproduce some of the color illustrations.

*Such references include:

Demis, D. J., Dobson, R. L., and McGuire, J. (eds.). *Clinical Dermatology*. Hagerstown, Md.: Harper & Row, 1981.

Fitzpatrick, T. B., Eisen, A. Z., Wolff, K., Freedberg, I. M., and Austen, K. F. (eds.). *Dermatology in General Medicine* (2nd ed.). New York: McGraw-Hill, 1979.

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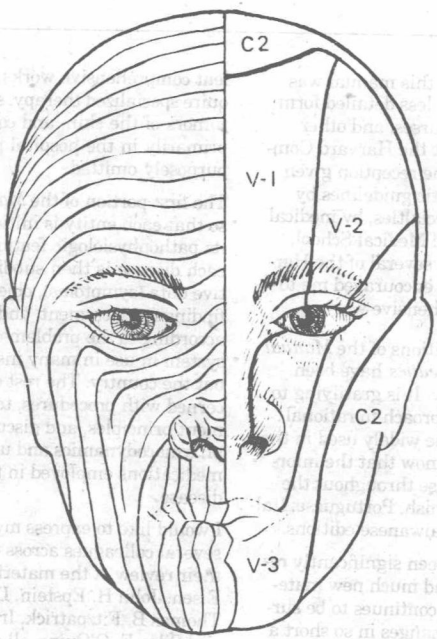
Rook, A., Wilkinson, D. S., and Ebling, F. J. G. (eds.). *Textbook of Dermatology* (3rd ed.). Oxford: Blackwell, 1979.



Left side: relaxed skin tension lines. Right side: dermatone chart—sensory root fields.

Note: The illustrations on the inside covers and facing back cover, dermatome charts and relaxed skin tension lines, represent approximations, since there is much overlap and individual variation. Denervation of one posterior root will *not* produce complete anesthesia within the corresponding dermatome. The direction of the relaxed skin tension lines (RSTL) should always be assessed before making an ellipsoidal incision parallel to, or a punch biopsy with skin stretched perpendicular to, these lines (see Fig. 1, p. 202). In areas of flexion creases, flex and note the direction of the majority of "wrinkle" lines, that is, the direction of the RSTL. In nonflexion areas, the RSTL is determined by picking up skin folds between thumb and index finger and pinching, proceeding in a clockwise direction, until it is clear in which direction wrinkle lines are most numerous, straight, and parallel to one another. In certain areas it is difficult or impossible to find the RSTL. In that situation, make a small circular incision or "punch" to see in which direction the ellipse forms.

Contents

Common dermatologic diseases: diagnosis and therapy

Notice. The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

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 age 8–10 at "sebarche" and are usually seen 2 years earlier in girls. Severe disease affects boys 10 times more frequently (up to 15% are involved), increases in prevalence steadily throughout adolescence, and then decreases in adulthood.

Severity of involvement can most often be correlated with the amount of sebum secreted; patients with severe acne will usually have large and active sebaceous glands with consequent prominent follicle 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 of normal persons.

Androgens are the only stimulus to sebaceous gland development and secretion, but acne patients do not have higher plasma levels of androgens. At puberty, hormonal stimuli lead to increased growth and development of sebaceous follicles. In those who develop acne there is presumably a heightened responsiveness of these glands to androgenic stimulation. This heightened end-organ response of the sebaceous glands results in increased conversion of testosterone to dihydrotestosterone (DHT) and other 5 alpha-reduced metabolites; acne-bearing skin has been shown to produce up to 20 times more DHT than normal skin for corresponding areas.

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 *Propionibacterium (Corynebacterium) acnes*, that acts as the primary irritating substance in inflammatory acne. In addition, *P. acnes* produces chemotactic factors that, together with those present in comedonal material, attract mononuclear cells. Patients with severe acne demonstrate cell-mediated immunity directed toward *P. acnes*, and 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. The

resultant 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"). Its dark color is due to oxidized lipid and to melanin within the mass of horny cells; this plug is **not** dirt. As follicle walls 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). 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. The spontaneous disappearance of acne may also be related to a decreased dermal reactivity to irritant substances.

As many as a 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 progestogens present in some oral contraceptives, by recent cessation of oral contraceptives ("postpill acne"), or from 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.

II. Subjective data

A. Patients' complaints may be related to inconspicuous lesions that nevertheless cause considerable social embarrassment. As with all medical and psychologic 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.

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- –2-mm white dot (whitehead) most easily seen when the skin is stretched. If follicle contents extrude, a 2- –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?

1. Are menstrual periods regular? Is there any hirsutism? (Stein-Leventhal syndrome, Cushing's syndrome, and other endocrinopathies are frequently accompanied by acne.) Men and women with severe cystic acne, especially those who do not respond to conventional therapy, may have elevated plasma testosterone and/or dehydroepiandrosterone sulfate levels.

2. Is there a premenstrual flare-up? The sebaceous duct orifice is significantly smaller between days 15–20 of the menstrual cycle, leading to increments in duct obstruction and resistance to flow of sebum. Many of these women tend to do well on anovulatory drugs.

3. Is the patient on oral contraceptives, or has she stopped taking these pills within the past few months? When were the pills started? Which ones? During the first two or three cycles on oral contraceptives acne may flare up. Postpill acne may continue for as long as a year after birth control pills are stopped. Although anovulatory drugs may provide excellent therapy for acne, the various pills differ enormously in their effect on the sebaceous gland (see p. 11). Oral contraceptives that contain the androgenic and antiestrogenic progestogens norgestrel, norethindrone, and norethindrone acetate may actually provoke an acneform eruption. Ovral is cited particularly frequently in this regard.

B. What is the effect of seasonal changes? Has the patient recently been in a hot and humid environment? Is sunlight beneficial? Most patients find that summer sunlight will diminish the activity of their acne. However, very humid environments or heavy sweating will lead to keratin hydration, swelling, decrease in the size of the sebaceous follicle orifice, and partial or total duct obstruction. It is thus not always good advice to "get out into the sun," except in a dry climate. A small number of people overly exposed to sunlight will develop an acneform papular eruption related to abnormal follicular keratinization ("Mallorca," miliary, actinic acne).

C. Is the patient exposed to heavy oils, greases, or tars? These comedogenic agents will initiate lesions, as can some greasy substances used for hair care (pomade acne). Certain oily or greasy cosmetics and creams can also exacerbate acne.

D. Does the patient wear occlusive or tight clothing or have any habits that will initiate or aggravate the disease? Mechanical trauma (pressure, friction, rubbing, squeezing) as from clothing or athletic wear or from behavioral habits will also cause lesions. For example, an individual with the habit of cradling the chin in his or her hand may develop unilateral lesions at that site.

E. Has the patient been on any medications known to cause acne? The most prominent among these are corticosteroids, ACTH, androgens, Danazole, iodides, and bromides. Other possible stimuli include trimethadione, Dilantin, INH, lithium, halothane, vitamin B_{12} cobalt irradiation, and hyperalimentation therapy. Corticosteroids, both systemic and topical, are not directly comedogenic; they do appear to sensitize—to "prime"—the follicular epithelium to the comedogenic effects of sebum. Steroid acne starts as uniform red papules, which are then succeeded by closed comedones, and later by open comedones. Chronic steroid acne shows all three types of lesions.

F. How has the patient's acne been treated in the past? Have antibiotics been used? If so, what were the instructions, dosage, duration, and effect of these therapies? Was tetracycline inadvertently taken with meals instead of on an empty stomach? Was the dosage adequate? (See Antibiotics, p. 9.)

An unusual complication of chronic tetracycline administration is the development of a **gram-negative folliculitis.** Such patients will notice a sudden change in their acne, with the appearance of pustules or large inflammatory cysts that, on culture, usually grow *Proteus, Pseudomonas,* or *Klebsiella* species. Since acne cysts are sterile on routine bacteriologic culture, a sudden change in morphology warrants Gram's stain and culture of cyst/abscess contents. Gram-negative folliculitis usually responds to ampicillin, 1 gm/day, after which tetracycline can again be started.

G. Is there any effect from stress or emotional upsets on acne activity? An acutely stressful situation may cause acne to flare up suddenly (but "nerves" are **not** the cause of the disease).

H. The number and type of lesions should be roughly quantitated in order to assess further therapeutic responses.

V. Therapy

A. Mild involvement (few to many comedones)

1. Bacteriostatics are thought to improve acne by decreasing the formation of harmful by-products, but not necessarily the actual number, of *P. acnes* bacteria. These should be applied twice daily to the point of mild dryness and erythema but not discomfort. The gel-based benzoyl peroxide products are the agents of choice for the usual case.

a. Benzoyl peroxide (see also p. 239) has a potent antimicrobial effect. It is hypothesized that this agent is decomposed by the cysteine present in skin, after which free radical oxygen is capable of oxidizing proteins in its vicinity. These proteins include the bacterial proteins of the sebaceous follicles, thus decreasing the number of *P. acnes* and consequently the amount of free fatty acids. Topical 5% benzoyl peroxide lowers FFA 50–60% after daily application for 14 days and decreases aerobic bacteria by 84% and anaerobic bacteria (primarily *P. acnes*) by 98%. Benzoyl peroxide will also reduce the size and number of comedones present and may inhibit sebum secretion. Contact sensitivity is observed in 1–3% of patients.

(1) Benzoyl peroxide products. Clear aqueous gel (Desquam-X); clear alcohol gel (Benzagel, PanOxyl); clear acetone gel (Persa-gel); clear oil-based lotion (Benoxyl, Persadox).

b. Topical antibiotics (see also p. 240) may affect acne lesions by their antibacterial action or because of suppressive effects on the inflammatory response. Papular and pustular lesions respond best; the activity of comedonal or cystic acne may not be altered. There are no studies comparing the relative effectiveness of these drugs. It would appear that clindamycin and erythromycin are easiest to use and probably most helpful, tetracycline next, and then meclocycline. All topical antibiotics are applied twice daily.

(1) Clindamycin phosphate is available in 1% concentration in a hydroalcoholic vehicle as Cleocin T lotion (30 ml or 60 ml). Cleocin hydrochloride solutions can be compounded extemporaneously by dissolving the contents of Cleocin capsules into other vehicles such as Neutrogena Vehicle N (e.g., four 150-mg capsule contents in 50-ml vehicle = 1.2%; contents of 8 capsules = 2.4%). The drug has not been detected in the blood after topical use, but there have been two reports of pseudomembranous colitis after topical use of clindamycin hydrochloride. Patients with inflammatory bowel disease should avoid topical clindamycin use and all patients should be warned to discontinue therapy if intestinal symptoms occur.

(2) Erythromycin base applied topically is moderately effective and nonsensitizing. It is available as 1.5% solution (Staticin, 60 ml); and 2.0% solution (Ery Derm, 60 ml, and A/T/S, 60 ml).

(3) Tetracycline hydrochloride (Topicycline, 70 ml) may produce a temporary yellow discoloration of the skin that may be washed off 1 hr after application with no decrease in drug effectiveness. Skin with tetracycline on the surface will fluoresce when viewed under long-wave ultraviolet light (e.g., black lights in discos). The serum level after continuous 2id application is 0.1 mcg/ml or less.

(4) Meclocycline sulfosalicylate, an oxytetracycline derivative, is the only topical antibiotic manufactured in a nonalcoholic, nonlotion base. Meclan Cream (20-gm tubes) is less drying, but has an unpleasant smell and may be less effective than other topical antibiotics.

c. Aluminum chloride hexahydrate (Xerac A-C) is an effective antiperspirant that also has an antibacterial effect. It may be useful in cases of acne in which sweating is prominent or appears to be aggravating the disease but its effects have not been well studied.

d. Although the administration of systemic antibiotics will reduce comedo formation in experimental animal systems these drugs play no role in the therapy of the usual patient with comedonal acne.

2. Exfoliants. These agents, such as elemental sulfur, resorcinol, and abrasives, produce irritation and consequent peeling and exfoliation. Not all topical irritants have the property of decreasing the presence or formation of new comedones. Most are a source of additional injury to already inflamed skin. Also, they are ineffective at removing comedones that are too deeply rooted to be affected by surface measures. Tretinoin is the most effective comedolytic agent, followed by salicylic acid and benzoyl peroxide.

a. **Abradant cleansers.** Apply 1–2id. These products incorporate finely divided particles with cleansers and wetting agents. They are not indicated in most cases but may be used in the patient who appears to respond to them empirically.

(1) **Products.** Polyethylene particle cleanser (Pernox scrub or lotion); aluminum oxide particle cleansers (Brasivol, fine, medium, rough); sodium tetraboxate decahydrate particle cleanser (Komex). These particles dissolve on use and thus their abrasiveness is limited.

b. **Topical exfoliants and irritants.** Clear gels or lotions (Acne Aid, Komed, Saligel, Transact; tinted creams (Acne Aid, Acnomel, Fostril, Sulforcin); tinted lotions (Acne Aid, Liquimat).

B. Mild or moderate involvement (few to many comedones, some papules and/or pustules)

1. Benzoyl peroxide gel, and/or

2. **Tretinoin** (trans-retinoic acid; vitamin A acid), the most effective comedolytic agent, used alone or in combination with benzoyl peroxide gels, may offer unique beneficial effects for those who can tolerate its use. The irritant effects of tretinoin sometimes limit its usefulness, but these can be minimized by the correct method of application. Tretinoin, which does not function as a vitamin in its therapeutic applications, increases epidermal cell turnover and decreases the cohesiveness ("stickiness") of horny cells, thus inhibiting the formation of comedones while helping existing comedones to become loosened and expelled. Tretinoin not only changes follicular keratinization, but decreases the number of normal cell layers of the stratum corneum from 14 to 5. This decrease in thickness of the barrier layer may potentiate the penetration of other topical agents.

a. **Instructions for use**

(1) Erythema and peeling—a mild flush—are the objects of therapy. More severe dryness is to be avoided. It is the achievement of a mild facial flush that is important, not specific adherence to a predetermined course of therapy.

(2) Fair-complexioned patients with easily irritated skin should start with the 0.05% cream or gel; others may use the 0.1% cream, or solution.

(3) All other topical acne agents must be stopped prior to initiating retinoic acid therapy. Use mild, gentle soaps no more than twice daily.

(4) Apply once daily lightly to all areas except around the eyes and lips. Apply approximately 1 hr before bedtime on thoroughly dry skin—wait for at least 15 min after the face has been washed.

(5) Avoid excessive exposure to sun. There is some experimental evidence that exposure to ultraviolet light in tretinoin-treated animals leads to an increased incidence of skin cancers, but this question is not yet resolved.

(6) Expect redness and peeling within a week, lasting 3–4 weeks,