Rosacea is a common skin condition that affects an estimated 13 million Americans, with almost half of these patients between the ages of 30 and 50 years old [1]. It is a relapsing, chronic dermatosis that develops in stages and is characterized by a defect in vascular responsiveness [2,3]. Most often, fair-skinned individuals are seen first with flushing and blushing episodes followed by persistent erythema and telangiectasia with later recurrent eruptions of inflammatory papules and pustules involving the central face. These lesions nearly always occur on a backdrop of solar elastosis and dermatoheliosis [4]. Although there is a greater incidence of the milder, earlier stages of rosacea in women, men more fre-
quenty have the more severe form (i.e., rhinophyma) [5]. In most cases of rosacea, the standard therapy can be augmented by the addition of glycolic acid peels and home application of lower concentration glycolic acid preparations.

I. PATHOGENESIS

The pathogenesis of rosacea is most likely multifactorial. It is a polymorphic disease that seems to be precipitated by many causes, including genetic, vascular, immune-mediated, emotional, environmental, and infectious factors. Central to disease formation is the development of vascular hyperresponsiveness in genetically predisposed individuals. Even features of rosacea other than erythema and telangiectasia may derive from this same vascular abnormality [2]. It is hypothesized that rosacea is preceded by the degeneration of perivascular, vascular collagen, and elastic tissues in susceptible persons when exposed to environmental stimuli like heat, humidity, friction, cold, or sunlight [4]. This deterioration can result in permanent dilation of dermal blood vessels (telangiectasia) with subsequent leakage of inflammatory mediators [2,4]. Elastin degradation caused by chronic actinic exposure may also lead to lymphatic insufficiency, which can create a sterile, low-grade dermal cellulitis [2]. All of these processes unfortunately promote even further flushing by means of vasodilatory mechanisms [2,4].

Other triggers precipitating flares of rosacea include emotional stimuli such as stress and excitement; physiological stimuli like exercise and ingestion of alcohol, hot beverages, and spicy foods; exogenous stimuli such as application of skin care products containing ingredients like alcohol, witch hazel, menthol, peppermint, eucalyptus and clove oils, or other potential irritants [1]. Factors that have been implicated in the development of rosacea include Demodex folliculorum mite infestation and Helicobacter pylori infection [6,7]. In one study, the mean Demodex mite count was significantly
higher in subjects with rosacea than in controls. It is hypothesized that an increased mite load may play a role in the pathogenesis of rosacea by provoking inflammatory or allergic reactions either by mechanical blockage of follicles or by acting as a vector for microorganisms [6]. Other researchers have noted that subclinical *H. pylori* infection may also be involved in the genesis of rosacea and that eradication treatment may reduce the severity of skin disease [7]. Another organism, *Malassezia furfur* (*Pityrosporum ovale*), which is routinely found on biopsy specimens of rosacea, may also play a role in pathogenesis. Unlike acne, the presence of bacteria within the hair follicle does not seem to affect rosacea [3].

II. CLINICAL STAGES

Rosacea can usually be subdivided into three clinical stages. Some patients may advance from mild to more severe disease, whereas others remain at a given stage. The first stage of rosacea is predominantly vascular. It is characterized by recurrent flushing on the central face, neck, and upper chest [2]. These brief episodes, which are usually provoked by the stimuli mentioned previously, slowly become less transient with time. Prolonged flushing also causes persistent facial edema to develop [2–4]. This chronic erythema and swelling are thought to be the result of increased numbers of erythrocytes within inflamed superficial vasculature [2]. Later, telangiectases also become prominent on the cheeks and nose.

The second stage, inflammatory rosacea, is marked by the appearance of crops of follicular-based inflammatory papules and pustules. In the background, there is persistent erythema, more numerous telangiectases, elastosis, dermatoheliosis, solar comedones, and prominent facial pores [2–4].

Only a minority of patients progress to the third stage, which is characterized by a proliferation of sebaceous, connective, and vascular tissue and results in bulbous hypertrophy of the nose called rhinophyma. These patients also have
deep persistent erythema, dense telangiectases, papules, and pustules. Facial contours may become coarse and thickened because of the massive deposition of collagen and sebaceous hyperplasia [4]. This last stage of rosacea is more commonly found in men [5].

III. HISTOPATHOLOGY

In stage one, there is mainly vascular dilation of the upper and middermal venules and lymphatic vessels, with some perivascular and perifollicular lymphohistiocytic inflammation [8]. There is also slight edema and some elastic tissue hyperplasia present.

Likewise, in stage two there is more significant lymphohistiocytic infiltration around the follicles and the vasculature. Pustules appear as intrafollicular collections of neutrophils and chronic folliculitis. Inflammation is also prominent around sebaceous structures. Venous thickening and dilation along with marked elastosis are noted as well [4,8].

The rhinophyma of stage three rosacea is seen as hyperplastic, irregular sebaceous follicles and widespread dermal fibroplasia with connective tissue proliferation. Sebaceous ducts are dilated and filled with sebum and keratinaceous debris. In all stages, *Demodex folliculorum* can be found within sebaceous ducts and follicular infundibula [8]. Likewise, in our experience *Malassezia furfur* is also commonly observed within hair follicles in the biopsy specimens of rosacea.

IV. INDICATIONS FOR TREATMENT WITH GLYCOLIC ACID

Alpha hydroxy acids such as glycolic acid can be useful in the treatment of rosacea. Although rosacea can be seen in many forms, photodamage seems to be an almost universal associated feature. Studies have shown that glycolic acid (GA) peels and topical preparations can help repair and reverse changes
such as fine wrinkling, coarse texture, and the overall severity of sun-damaged skin [9,10]. Furthermore, glycolic acid treatment can also provide a protective anti-inflammatory action by acting as an antioxidant in photodamaged skin [11]. Histological effects of GA treatment include reduction of stratum corneum thickness, increased epidermal thickness, more orderly differentiation, enhanced rete ridge pattern, and dispersal of melanin within the basal layer [12–14]. In addition, alpha hydroxy acid improvements within the dermis include a thickened papillary dermis, increased collagen synthesis, increased hyaluronic acid levels, and an increased amount and improved quality of elastic fiber tissue [12–16]. A recent study revealed that glycolic acid treatment, both in vitro and in vivo, increased the production of collagen by means of a direct effect on fibroblast proliferation that is independent of inflammatory mechanisms [17]. In patients with inflammatory lesions such as papules and pustules, GA peels can be an important adjunctive therapy. They act by promoting spontaneous “unroofing” of pustules by means of subcorneal epidermolysis secondary to more rapid penetration of acid through the thin epidermis and stratum corneum overlying the lesions [14].

Concerns regarding the compatibility of potentially irritating agents such as alpha hydroxy acids and the sensitive skin of rosacea patients are recognized. However, we have safely treated numerous rosacea patients in our clinics with GA peels and topical preparations. Recently, we performed an open-label, 12-week pilot study that investigated the safety and efficacy of gluconolactone, a new poly hydroxy acid, products on 15 women with rosacea. Exuviance® sensitive skin care products by NeoStrata, Inc.: Daytime Cream SPF 15 (gluconolactone 4%, pH 3.8) and Evening Cream (gluconolactone 8%, pH 3.8) were applied respectively in the morning and before bedtime. Significant improvement, as evaluated by physician clinical assessment, was noted for the following parameters: texture, fine lines, overall photodamage, dryness, and erythema. Similarly, 80% of patients rated the products
as good to excellent in cosmetic acceptability [18]. (Figs. 5.1, 5.2, see color insert.)

In a safety assessment by the Cosmetic Ingredient Review (CIR), it was determined that even on normal skin alpha hydroxy acid ingredients can be dermal irritants. As expected at a given pH, higher concentrations of GA preparations tended to increase irritation. Meanwhile, an inverse relationship existed between the pH of the GA product and amount of irritation produced [19]. In most over-the-counter cosmetic products, the irritant potential of alpha hydroxy acids can be dampened by the vehicle and pH adjustors such as salts of the acids. The CIR also reported that GA and lactic acid, their common salts and simple esters, were safe for the use in cosmetic products at concentrations ≤10%, at final formulation pH ≥3.5. Cosmetic products for over-the-counter use include toners (astringents), cleansers, lotions, and creams. These same ingredients were deemed safe for use in salon-applied products at concentrations ≤30%, at a final concentration ≥3.0 in products designed for brief, discontinuous use followed by rinsing [19]. Designated salon-applied products are superficial alpha hydroxy acid chemical peels.

Because GA and other agents are potentially irritating, it is clear that special care must be taken by the dermatologist when selecting an alpha hydroxy acid regimen for the sensitive skin of rosacea patients. Our clinical and research study findings have confirmed that superficial peeling agents like GA can be safely and effectively used in the treatment of rosacea.

V. TREATMENT REGIMENS FOR ROSACEA

A. Flushing

Flushing is often the most troublesome symptom among rosacea patients. Because there are numerous “triggers” that may bring about a rosacea flare, it is important for patients to
avoid these factors (environmental, food-related, psychological, and contact) that provoke flushing and other symptoms. Although no medication can completely suppress physiological flushing, some patients are helped by anticholinergics such as glycopyrrolate (at a dose of 2 mg b.i.d., whereas others may benefit from beta-blockers such as propranolol and naldolol or alpha-agonists like clonidine patches [20]. Sunscreens or sunblocks should also be used to prevent further photodamage and dilation of cutaneous vessels. Foundations and other makeup should be chosen to provide both adequate camouflage and sun protection (SPF 15 or greater) with minimal irritation. For patients with marked flushing and erythema, we often suggest a foundation cover-up with a green tint. Repeated laser treatments can also be helpful for persistent erythema and telangiectases.

B. Inflammatory Papules and Pustules

1. Antibiotics

Initial therapy for rosacea generally consists of a topical antibiotic metronidazole with or without an oral antibiotic in the tetracycline family, depending on the severity of the condition [21]. The mechanism of action of antibiotics in rosacea is most likely anti-inflammatory rather than antibacterial. Topical metronidazole (Metrogel™, Metrolotion™, and Metrocream™, 0.75% for b.i.d. application, and Noritate™, 1.0% for q.d. application) can be selected according to patient skin type. The mechanism of action of metronidazole has been attributed to antibiotic/antiparasitic activity on *Demodex folliculorum*. It also displays anti-inflammatory activity and immunosuppressive effects, being responsible for the inhibition of localized cutaneous cell-mediated immunity [22]. Alternate or additional topical antibiotics include sulfacetamide with or without sulfur (Sulfacet-R™ or Klaron™). These sulfur-based agents may help kill *Demodex* mites, as well as being anti-in-
Inflammatory [20]. Topical clindamycin and erythromycin are also effective in rosacea.

Tetracycline, in doses of 250 to 500 mg b.i.d., or minocycline, in doses of 50 to 100 mg b.i.d., are often started with topical metronidazole in hopes of hastening recovery [20]. The therapeutic activity of the tetracyclines seems to be related to their anti-inflammatory effects. They also reduce neutrophil chemotaxis and macrophage phagocytosis, while also inhibiting complement activation and immune-mediated reactions [22]. Alternate oral agents include doxycycline, ampicillin, amoxicillin, clarithromycin, erythromycin, trimethoprim/sulfamethoxyazole, and metronidazole [20,22].

A recent study demonstrated that continued treatment with metronidazole alone can maintain remission of moderate to severe rosacea induced by treatment with oral tetracycline (250 mg q.i.d. for 12 weeks followed by a 4-week taper) and topical metronidazole 0.75% gel (b.i.d. application) [21].

2. Glycolic Acid

In our patients with stage one to two rosacea, we find that taking a combination approach by adding GA peels and topical GA products to an antibiotic regimen can dramatically improve the patient’s condition.

Although the GA peels tend to provide maximal benefit for the inflammatory lesions and background photodamage, home application GA cleansers and lotions can help maintain the resultant positive changes. We try to tailor the regimen to the individual patient. In many cases, individual products of the “program” may be changed, depending on the particular needs and sensitivities of the patient’s skin.

Over-the-counter GA products can be divided into the following categories: toners, cleansers, creams, and lotions. The purpose of a toners or astringents is to remove excess oil and temporarily tighten skin. Although most toners are now alcohol-free, ingredients like GA will still have a significant drying
effect on the skin. Cleansers containing GA have a dual pur-
pose in that they remove excess oil and tighten skin while also
promoting gentle exfoliation. Glycolic acid–containing creams
and lotions confer some degree of moisture to the skin while
also suppressing acne and rosacea lesions by diminishing cor-
neocyte cohesion and promoting normal keratinization.

For at least a month before initiating the GA peel series,
we like our patients to use a GA-containing cleanser and oil-
free, noncomedogenic GA lotion to prepare the skin. In our
experience, topical preparations such as the MD Forte® facial
cleanser and facial lotion, which have a 15% GA concentration
and have been partially neutralized to a pH of 3.8, are effica-
cious and have low irritation rates in our rosacea patients.
Patients will generally start out with once-daily cleansing and
lotion application and work up to twice-daily use as tolerated.

After consistent application of GA products for 4 to 6
weeks with minimal to no irritation, we begin with the GA
Peels. The Gly Derm® line of GA peels (“glycolic applicators”) is well suited to the variable sensitivities of rosacea patients,
because it comes in concentrations ranging from 20–70% and
delivers a fixed quantity of GA per packet. The lowest con-
centration peel (20%) has a product pH of 1.4; whereas the
highest concentration peel (70%) has a product pH of 0.1.

Before the peel, the patient’s face is first prepared by
cleansing with the Gly Derm gentle cleanser (GA concen-
tration, 2%; pH, 5.7). Next, we lightly swab the area with an al-
cohol pad followed by acetone solution to degrease the skin.
Initially, this part of the process is performed on a small area
of the forehead to test for any potential irritation. If a patient
does display some sensitivity, this step is foregone in the fu-
ture. Now the glycolic peel is applied. Special care is taken to
avoid excess rubbing, which would otherwise potentiate un-
even absorption and undue irritation.

The length of contact time must be determined on an in-
dividual basis. Generally, for the first peel we allow half of the
recommended time (2–3 min) to elapse before having the pa-
tient rinse her face with tepid water. We can then gauge her
degree of sensitivity and determine which concentration and
the length of exposure to use subsequently. The interval be-
tween peels is also variable, ranging from 2 to 4 weeks. For
optimal effect, we suggest a series of six to eight peels. Be-
tween peels and after completion of the series, patients con-
tinue to use their topical GA products. “Touch-up” peels may
be performed at more distant intervals as they are required.
(Figs. 5.3, 5.4, see color insert.)

3. Tretinoin

Tretinoin, a vitamin A derivative, has been shown to influ-
ence epidermal keratinization, reverse gross and microscopic
changes of photoaging, and modulate epidermal differentia-
tion and wound healing. It has long been used in the treat-
ment of acne vulgaris and photoaged skin. Lower strength
(0.025%) tretinoin (Retin-A™) cream applied nightly for 16
weeks has been shown to be beneficial in the treatment of se-
vere or recalcitrant rosacea. Therapeutic benefits were mea-
ured in terms of reduction of papules, pustules, and erythe-
ma. Using a lower concentration of tretinoin can minimize the
adverse effects such as dryness, stinging, scaling, and erythe-
ma seen with use of higher strength preparations [23]. In our
experience, the benefits of tretinoin in rosacea can best be
achieved using the lowest concentration of tretinoin, 0.025%,
cream and decreasing the frequency of nightly application to
two to three times per week. Irritation may further reduced
by diluting the tretinoin with an oil-free moisturizer before
use.

4. Isotretinoin

When rosacea is recalcitrant, isotretinoin in doses of 0.2–0.5
mg/kg/d has been used with good results [4]. The treatment
period is usually between 3 and 5 months. Studies report pri-
mary improvement in inflammatory lesions, edema, and
rhinophyma but negligible effect on erythema [4,24]. Because isotretinoin’s mode of action is to alter keratinization in the skin and reduce sebaceous gland size by decreasing proliferation of basal sebocytes and suppressing sebum production, it is of particular benefit in patients with oily, large-pored skin with multiple sebaceous gland hyperplasias. Isotretinoin has also been shown to have anti-inflammatory, immunomodulatory, and antiangiogenic properties [24]. In addition to treating acne and rosacea, isotretinoin has been shown to be efficacious in cases of severe seborrhea and gram-negative folliculitis, which suggests a broad-spectrum antimicrobial effect. It may also have an effect on decreasing adrenal gland function.

As with any isotretinoin treatment regimen, full explanation of all potential adverse effects, especially teratogenicity, should be discussed before hand with the patient. Routine laboratory monitoring of liver function tests, lipids (cholesterol, triglycerides), qualitative beta-human chorionic gonadotropin levels (if applicable), and complete blood count should be performed at baseline and at 4- to 6-week intervals while on therapy. Unfortunately, some patients may note relapse of their rosacea once isotretinoin is withdrawn. Nonetheless, isotretinoin has a necessary place in managing the most severe or persistent cases.

C. Laser Surgery

Although peels predominantly improve underlying photodamage and inflammatory lesions, persistent erythema and telangiectases are best handled with laser surgery. For patients who have discrete sprays of telangiectases, effective vessel elimination can be achieved with the Versapulse (532 nm) laser. When persistent diffuse erythema and telangiectases are the problem, treatment with the flash-lamp-pumped tunable dye laser is preferable [25]. Most patients require at least 3 to 10 treatments to clear most of their vas-
cular lesions. Interestingly, ablation of dilated vessels with the laser has been shown to reduce the number of subsequent inflammatory lesions [2,25].

With the rise of CO₂ resurfacing laser use, excellent cosmetic results have been obtained in patients with severe, disfiguring rhinophyma. Other surgical modalities include electrotherapy, dermabrasion, excision and skin grafting, scalpel shaving, and cryosurgery. Isotretinoin is often used preoperatively to shrink bulbous portions and is frequently continued postoperatively to maintain the improvement [4].

VI. CONCLUSION

In summary, rosacea is a potentially progressive, chronic dermatosis that deserves early and aggressive therapy. It is a polymorphic disease that is affected by genetic, vascular, immune-related, psychological, environmental, and infectious factors. With prompt intervention, patients can expect control of their symptoms and a significant improvement in the appearance of their skin. Because the manifestations of rosacea can range from vascular to inflammatory, optimal management should target treatment toward the specific lesion. The need to minimize or avoid contact with triggers that provoke flares of rosacea should be emphasized. Although laser surgery is the most effective treatment for persistent erythema and telangiectases, topical and oral antibiotics are the cornerstones of initial therapy for papulopustular lesions. Treatment of background photodamage, which is characteristic of all stages of rosacea, and mild to persistent inflammatory lesions can be augmented by the addition of a GA program. The synergistic combination of antibiotics and GA is highly effective and well tolerated by most all rosacea patients. Because alpha hydroxy acids can be potentially irritating, it is of paramount importance that the dermatologist carefully design a regimen that will have maximal efficacy with minimal adverse cutaneous effects. Collectively, a series of GA peels used in
combination with daily use of GA cleanser and lotion will work above, below, and at the surface of the epidermis to rejuvenate and repair the stigmata of rosacea.

REFERENCES


