

## Rosacea: II. Therapy

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Despite an incomplete understanding of the pathogenesis of rosacea, therapeutic modalities continue to expand. The principal subtypes of rosacea include erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea. These phenotypic expressions are probably caused by divergent pathogenic factors and consequently respond to different therapeutic regimens. A subtype-directed approach to therapy is discussed in part II of this review. We provide an overview of the available topical, oral, laser, and light therapies in the context of these cutaneous subtypes, review the evidence that supports their use, and outline their therapeutic approach. Suggestions for future areas of study also are provided. (*J Am Acad Dermatol* 2004;51:499-512.)

**Learning objective:** At the completion of this learning activity, participants should be familiar with the subtype-directed approach to therapy for rosacea including available topical, oral, laser, and light therapies.

Prior to initiating therapy, a dermatologist should assist patients in identifying factors that trigger their signs and symptoms. Trigger factors are specific for each patient, and common triggers do not affect every patient. They include hot or cold temperature, wind, hot drinks, exercise, spicy food, alcohol, emotions, topical products that irritate the skin or impair barrier function, menopausal flushing, and medications that promote flushing. Those factors that induce flushing should be avoided if feasible. Other key aspects of prevention include the daily use of a broad-spectrum, gentle sunscreen, avoidance of midday sun, seeking shade, and the use of protective clothing. The signs and symptoms of rosacea may be camouflaged with nonirritating cosmetics and concealers.

### SUNSCREEN

Practicing sun avoidance behaviors is of central importance to rosacea management. In addition, a broad-spectrum sunscreen should be applied daily. The physical blockers titanium dioxide and zinc oxide are well tolerated by most patients. General guidelines for the use of sunscreens by persons with rosacea are provided in Table I. Several rosacea creams contain sunscreen ingredients. A combination sunscreen and 1% metronidazole is now

marketed in Canada as Rosasol cream (Stiefel Canada, Inc, Montreal, Quebec).<sup>1</sup> Unfortunately, some sunscreens can trigger cutaneous irritation and produce erythema. Protective ingredients such as silicones should be included in sunscreen preparations to minimize stinging and erythema. In the form of dimethicone or cyclomethicone, silicones are nonirritating and nonacnegenic occlusive agents that retard transepidermal water loss, impart water-resistant properties to cosmetics, and enable them to spread easily over the skin.<sup>2</sup> Rosac cream (Stiefel Laboratories, Inc, Coral Gables, FL), a combination of sodium sulfacetamide 10% and sulfur 5%, Parsol 1789, and other sunscreens in a dimethicone vehicle, is now available in the United States.

Nichols et al studied the irritant potential of various chemical sunscreen agents in patients with rosacea. They conducted a cheek-versus-cheek comparison of 4 test lotions and used a 4-point scale to score stinging at 1 minute.<sup>3</sup> Padimate O without dimethicone or cyclomethicone was significantly more irritating than a *p*-aminobenzoic acid-free sunscreen that contained both silicones ( $P = .0267$ ). However, the addition of dimethicone and cyclomethicone to the padimate O sunscreen reduced its irritancy, making it equivalent to the *p*-aminobenzoic acid-free lotion ( $P = .78$ ). Nichols et al concluded that the presence or absence of protective ingredients was more important than the presence or absence of *p*-aminobenzoic acid.<sup>3</sup>

### COSMETICS

Cosmetic intolerance and facial skin "sensitivity" are common features of the erythematotelangiectatic

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**Table I.** Guidelines for the use of sunscreen and cosmetics in rosacea patients with sensitive skin and barrier dysfunction

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Cleansers should be soap free.
Choose sunscreens that protect against ultraviolet A and ultraviolet B light. "Physical blockers" (titanium dioxide and zinc oxide) are best tolerated.
Cosmetics and sunscreens should contain protective silicones (dimethicone or cyclomethicone).
Choose a light foundation that is easy to spread and can be set with powder. (Foundations that contain ultraviolet A—ultraviolet B sunscreen are encouraged.)
Green-tinted makeup or sunscreen can provide extra coverage of red areas.
Avoid astringents, toners, menthols, camphor, and products that contain sodium lauryl sulfate.
Avoid waterproof cosmetics and heavy foundations that are harder to apply and remove without irritating solvents.

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and papulopustular subtypes of rosacea. In a series of 32 rosacea patients, 75% experienced stinging after application of 5% lactic acid, compared with 19% of 32 control patients.<sup>4</sup> All 7 erythematotelangiectatic patients experienced stinging, as did 17 of 25 papulopustular patients. It is common for many cosmetic formulations to dry and irritate rosacea-prone skin, possibly because of barrier dysfunction or vascular hyperreactivity.<sup>4-6</sup> Instructing patients to avoid irritating ingredients is not effective because it is often the interaction among chemicals or their concentration, not their presence, that promotes cutaneous irritation.<sup>7</sup>

A few formulations are problematic for the sensitive skin of erythematotelangiectatic and papulopustular patients, and a warning to avoid them is appropriate. Astringents, toners, menthol, and camphor-containing products are examples. Patients should similarly avoid products that contain sodium lauryl sulfate, an irritating anionic surfactant.<sup>7</sup> Table I provides guidelines for cosmetic use in patients with rosacea. Cleansers should be soap free, and products should be applied with the fingers to reduce barrier disruption.<sup>7,8</sup> Removal of waterproof cosmetics and heavy foundations is difficult without irritating solvents and should be avoided. Instead, light foundations that can be set with powder are recommended.<sup>7</sup> Ideally, a light liquid foundation makeup should contain a silicone for barrier protection in addition to a broad-spectrum sunscreen. Green-tinted makeup may also be used for extra coverage of red areas. Patients should first apply the green tint to red areas, then apply a layer of foundation makeup.

In addition to the avoidance of harsh products, patients with cosmetic intolerance and barrier sensitivity should be encouraged to apply a protective, gentle emollient to the face once or twice daily, preferably before the application of other products. Substantial decreases in papule counts and erythema have been routinely identified as placebo effects in randomized, controlled trials of numerous topical rosacea therapies versus emollient cream vehicles. Repair and protection of the stratum corneum represents an important adjunct for rosacea patients with barrier deficiency.

### TOPICAL MEDICATIONS

Three topical medications have been approved by the Food and Drug Administration (FDA) for rosacea. All are indicated for the management of papules, pustules, and erythema. They include 3 varieties of 0.75% metronidazole (Metrocream, Metrogel, and Metro lotion, Galderma Laboratories, Fort Worth, Tex) and 1% metronidazole (Noritate cream, Dermik Laboratories, Berwyn, Pa), several brands of 10% sodium sulfacetamide with 5% sulfur (Sulfacet-R tinted and tint-free lotions, Dermik Laboratories, Berwyn, Pa; Plexion cleanser and topical suspension, Medicis Pharmaceutical Corporation, Scottsdale, Az; Rosanil cleanser, Galderma Laboratories, Fort Worth, Tex; Rosula lotion, Doak Dermatologics, Fairfield, NJ; Clenia foaming cleanser and emollient cream, Upsher-Smith, Minneapolis, Minn; Rosac cream, Stiefel Laboratories, Inc, Coral Gables, Fla; Avar Green color corrective gel, CollaGenex Pharmaceuticals, Inc, Newtown, Pa) and 15% azelaic acid gel (Finacea, Berlex Laboratories, Montville, NJ). Several other topical medications are used off label for rosacea.

### METRONIDAZOLE

Pye and Burton first reported success with oral metronidazole for rosacea in 1976.<sup>9</sup> Nielsen was the first to demonstrate the effectiveness of a topical metronidazole formulation for rosacea during the early 1980s.<sup>10-12</sup> Over the years, debate has surrounded its most effective strength and dosing regimen. The 0.75% formulation was marketed first in the United States, and optimal dosing was determined to be twice daily, based on a half-life of 6 hours for the gel formulation.<sup>13</sup> Dahl et al later established the effectiveness of once-daily dosing, independent of strength. In a multicenter, 12-week randomized trial that included 72 patients, Dahl et al found no significant difference between once-daily application of the 1% and 0.75% formulations with respect to reduction of erythema, papules, and pustules; global assessment of severity; dryness;

treatment failure; and safety.<sup>13</sup> Topical metronidazole is rated B in pregnancy category.

Many double-blind, placebo-controlled trials of topical metronidazole have demonstrated beneficial effects in the treatment of rosacea.<sup>10-12,14-20</sup> Breneman et al compared the efficacy of once-daily metronidazole 1% cream with that of the vehicle alone in 139 patients. Significant reductions in inflammatory lesions were reached at 4 weeks.<sup>19</sup> Erythema reduction has been demonstrated in multiple studies,<sup>10,13,14,19-21</sup> but there is conflict regarding the onset of effect. Erythema reduction with metronidazole 1% daily therapy has reached significance as early as week 2<sup>20</sup> and as late as week 10,<sup>19</sup> depending on the series. Vehicle cream alone (applied twice daily) achieved a 28% reduction in the erythema score in one trial.<sup>20</sup>

The effectiveness of topical metronidazole has been favorably compared to that of low-dose tetracycline therapy, although tetracyclines achieve a faster clinical response.<sup>22</sup> In a double-blind study of 51 patients with rosacea, 1% metronidazole (plus placebo tablet) was compared with oxytetracycline (250 mg twice daily, plus placebo cream).<sup>10</sup> There was no difference in objective or subjective improvement between the 2 groups after 2 months of therapy. After discontinuation of oral therapy, topical metronidazole appears to maintain remission better than the vehicle alone, as demonstrated in a multicenter, randomized, double-blind trial in which 23% of 39 subjects who underwent maintenance with metronidazole gel experienced relapse, versus 42% of 43 subjects who applied a vehicle gel ( $P < .05$ ).<sup>8,23</sup> Other data have supported this finding.<sup>12</sup>

### SODIUM SULFACETAMIDE AND SULFUR

Sodium sulfacetamide 10% and sulfur 5% in combination have undergone a resurgence recently in the treatment of both acne and rosacea. The combination is in pregnancy category C. For more than 50 years, it has provided a safe, well-tolerated, and effective option for the treatment of acne vulgaris, rosacea, perioral dermatitis, and seborrheic dermatitis.<sup>24,25</sup> The use of sodium sulfacetamide and sulfur combinations is contraindicated in patients with sulfonamide hypersensitivity and in patients with kidney disease.

Sauder et al conducted an 8-week double-blind, placebo-controlled trial in 94 rosacea patients to evaluate the effectiveness of sodium sulfacetamide and sulfur lotion for rosacea.<sup>26</sup> At week 8, inflammatory lesions were decreased by 78% in patients who applied the sodium sulfacetamide and sulfur lotion, compared with a 36% decrease in patients given placebo. Erythema decreased 83% from baseline in

the sodium sulfacetamide–sulfur group versus 31% in control patients. Lebowhl et al evaluated the combination lotion versus metronidazole 0.75% gel in an investigator-blinded trial of 63 patients with rosacea over 8 weeks.<sup>27</sup> On the basis of physician global assessment at weeks 6 and 8, the sodium sulfacetamide–sulfur group achieved significantly lower papule and pustule scores, erythema scores, and overall severity ratings compared with the metronidazole gel group. Adverse reactions (pruritus, contact dermatitis, irritation, and xerosis) related to sodium sulfacetamide–sulfur occurred in 19% of patients and were mild.<sup>27</sup>

Twice-daily *cleansing* with sodium sulfacetamide 10% and sulfur 5% was evaluated alone and in combination with metronidazole therapy (0.75%) in an 8-week investigator-blinded controlled study of moderate rosacea in 30 patients.<sup>22</sup> The cleanser was an effective monotherapy, achieving significant reductions of papule counts and erythema. However, the combination of sodium sulfacetamide–sulfur cleanser followed by metronidazole cream was superior to the cleanser alone in the reduction of papule counts and overall rosacea severity.

Benefits of the newer “wash-on–wash-off” sodium sulfacetamide–sulfur formulations include easy incorporation as a combination modality, less lingering odor, lower irritation potential, improved absorption through hydrated skin,<sup>28</sup> and fewer interactions with other topical regimens or cosmetics. Masking fragrances are added to many of the topical “leave on” sulfur formulations, but their characteristic odor does reappear gradually after application.

### AZELAIC ACID

The FDA approved azelaic acid 15% gel (Finacea) in December 2002 for the treatment of mild to moderate rosacea. Azelaic acid is a naturally occurring saturated dicarboxylic acid.<sup>29</sup> Like metronidazole, azelaic acid is thought to inhibit or reduce the production of reactive oxygen species by neutrophils.<sup>30</sup> It is in pregnancy category B.

Two phase III vehicle-controlled, randomized trials have demonstrated the effectiveness and safety of 15% azelaic acid gel in 664 patients with papulopustular rosacea.<sup>31</sup> Improvement of erythema occurred in 44% and 46% of patients in the azelaic acid groups versus 29% and 28% of vehicle-treated patients. The mean reductions of inflammatory lesions in the azelaic acid–treated patients were 58% and 51%, versus 40% and 39% in control patients. At baseline, two-thirds of patients in both treatment groups reported skin dryness. Thirty-eight percent of patients who underwent treatment with azelaic acid experienced burning, stinging, or itching

related to the therapy, and these symptoms were transient in 70% of those affected. Approximately 12% of patients experienced scaling, skin dryness, or rash with the use of azelaic acid gel.<sup>31</sup>

In a smaller double-blind, randomized, split-face trial of 40 patients with papulopustular rosacea, the effectiveness of 20% azelaic acid cream was compared with that of topical metronidazole 0.75% cream over a 15-week period.<sup>32</sup> Papule and pustule counts were decreased by 78.5% in the azelaic acid group, compared with 69.4% in the metronidazole group. Most patients (92%) said they would continue to use azelaic acid, although transient stinging did occur in some patients.<sup>22,32</sup>

### **BENZOYL PEROXIDE**

Benzoyl peroxide can trigger stinging and erythema in some rosacea patients with barrier dysfunction and "sensitive" skin. In contrast, rapid resolution of erythematous papules and pustules can be achieved in nonsensitive patients (personal observation, M.T.P., W.D.J.), and a recent trial of benzoyl peroxide-clindamycin combination therapy has shown promise in patients with moderate rosacea (data in press, personal communication with James P. Leyden, MD). With few exceptions, patients with phymatous and glandular rosacea tolerate the drug quite well, and their inflammatory disease can often be controlled with benzoyl peroxide or benzoyl peroxide-clindamycin combination therapy. Benzoyl peroxide is in pregnancy category C.

### **ERYTHROMYCIN AND CLINDAMYCIN**

Mills and Klighman originally described the use of topical erythromycin base for the treatment of rosacea in 1976, when they were prompted by their successful results in acne vulgaris.<sup>33</sup> After 4 weeks of twice-daily topical erythromycin (in a vehicle of equal parts water and ethanol), reduction of erythema and suppression of papules and pustules were noted in 13 of 15 patients.<sup>33</sup> Side effects included transient stinging and dryness.

Clindamycin lotion is less popular for rosacea but has been compared favorably to oral tetracycline therapy in an investigator-blinded 12-week trial of 43 patients. Topical clindamycin (twice daily) produced clearance that was similar to oral tetracycline (1,000 mg/d for 3 weeks, tapered to 500 mg/d for 9 weeks), and topical clindamycin was more effective than tetracycline for the eradication of pustules.<sup>34</sup> Both erythromycin and clindamycin are in pregnancy category B.

### **TACROLIMUS**

Topical tacrolimus has been reported to be an effective treatment for steroid-induced rosacea-like eruptions.<sup>35,36</sup> Tacrolimus 0.1% ointment (Protopic, Fujisawa Healthcare, Inc, Deerfield, IL) is a macrolide nonsteroidal immunomodulatory agent approved in the United States for the treatment of atopic dermatitis. Goldman treated 3 patients with steroid-induced rosacea-like eruption using a 0.075% tacrolimus preparation twice daily for 7 to 10 days.<sup>35</sup> None of his patients was given oral tetracyclines concomitantly, but they were instructed to avoid topical steroids and rosacea triggers. Goldman noted that pruritus, erythema, and tenderness were resolved in each patient at the end of the 10-day treatment period.<sup>35</sup> Our observation in many such patients affirms the utility of tacrolimus; we find that using tacrolimus twice daily combined with 100 mg of minocycline twice daily for 1 to 2 months clears most patients.

### **TRETINOIN**

Dermal inflammation, elastin and collagen degeneration, and alteration of the cutaneous vasculature are the prominent histologic features of rosacea.<sup>37-39</sup> Topical tretinoin promotes connective tissue remodeling in the papillary and reticular dermis and minimizes dermal inflammation with chronic therapy.<sup>40-42</sup> Therefore, it is not surprising that topical retinoids have demonstrated benefit for rosacea, although their clinical response is delayed, often not evident until 2 or more months into therapy.<sup>43-45</sup> Ertl and colleagues noted the delayed response in 20 rosacea patients who underwent treatment with an oral or topical retinoid, or both, for 8 months, although their study was not well controlled. They noted improvement after 8 weeks of topical tretinoin monotherapy and after 4 weeks of isotretinoin, alone or in combination with tretinoin.<sup>46</sup> Their study included patients with "erythema with significant papules and/or pustules" and those with "disease activity incompletely controlled by prior therapies," including patients with "only modest numbers of inflammatory lesions."<sup>46</sup>

In 1999 Vienne et al treated 23 women with "mild" rosacea (10 patients with diffuse erythema, 10 with erythema and telangiectasia, and 3 with only telangiectasia) with 0.05% retinaldehyde cream.<sup>45</sup> Retinaldehyde was used instead of retinoic acid because of its better tolerability.<sup>47,48</sup> Facial erythema was measured with a spectrophotometer (Chromameter CR 200, Minolta, Tokyo, Japan). All patients completed the 6-month study with minimal signs of irritation. At 4 weeks a 10% decrease in

erythema was detected by means of spectrophotometry.<sup>45</sup> At 5 months a clinical response was noted in 75% of the 20 patients with erythema ( $P < .05$ ). Patients with only telangiectasia showed a lesser response.

Despite their intuitive appeal for rosacea based on histologic findings and positive observations in a few small series,<sup>43,46,49</sup> topical retinoids have been avoided because of their potential for irritation and concerns regarding possible promotion of angiogenesis.<sup>50,51</sup> It has been suggested that the use of tretinoin in rosacea may promote the development of telangiectasia by stimulating cutaneous neovascularization.<sup>44,50</sup> In 1993 Kligman described "noteworthy" angiogenesis in tretinoin-treated, non-sun-exposed skin of the elderly.<sup>44</sup> However, his findings were not accompanied by a visible increase in cutaneous vascularity or the development of telangiectasia. Vienne et al did not observe an increase in telangiectasia in their patients after 6 months of retinaldehyde therapy, although longer-term follow-up was not provided.<sup>45</sup> Likewise, years of topical tretinoin therapy in thousands of patients with facial photoaging have not uncovered a tendency for tretinoin to promote telangiectases. In fact the inhibitory effects of retinoids on vascular endothelial growth factor production by cultured human skin keratinocytes have been described; those effects occur via their anti-AP1 transcription factor activity.<sup>41,52</sup> Indeed, their antiangiogenic properties contribute partly to their success as antineoplastic agents.<sup>53</sup> Tretinoin is in pregnancy class C.

## ORAL MEDICATIONS

### Tetracyclines

Tetracycline has been a mainstay of rosacea therapeutics for more than 40 years, although it has not been approved by the FDA for treatment of this condition. Sneddon performed a double-blind, placebo-controlled trial of tetracycline for rosacea in 1966 to evaluate its effects on the "erythematous and papular type" and the "pustular form" of rosacea.<sup>54</sup> He treated 78 patients with either tetracycline, 250 mg twice daily, or placebo for 4 weeks, followed by a 4-week period during which all patients underwent treatment with tetracycline. At 1 month, 78% of the tetracycline-treated patients had improvement, whereas 45% of the placebo-treated patients did. During the second month, improvement occurred in an additional 74% of patients who had not previously received tetracycline. Eleven percent of the patients given tetracycline for 8 weeks had no improvement.<sup>54</sup> In those patients, "redness rather than pustulation was the main element of [their] rosacea."

A 3- to 4-week course of oral tetracycline is generally required to achieve substantial improvement in signs and symptoms.<sup>37,54</sup> Both Marks and Sneddon noted that clearance of rosacea could be achieved at subantimicrobial dosages,<sup>37,54</sup> and Marks added that "it is probable that the action of tetracycline in rosacea is not antibacterial." Sneddon achieved good maintenance with 250 mg daily or with 250 mg every other day, but he noted frequent relapses upon stopping the drug.<sup>54</sup> Knight and Vickers studied 68 rosacea patients and reported a 24% relapse rate within 1 month of tetracycline withdrawal (250 mg twice daily). Within 6 months after stopping therapy, 60% of their patients had recurrences.<sup>55</sup> The authors did not consider residual erythema active disease. Thirty-one percent of their patients maintained remission off therapy after 4 years of follow-up.<sup>55</sup>

The second-generation tetracyclines, which include minocycline, doxycycline hyclate, and doxycycline monohydrate, are similarly effective for rosacea, although controlled trials are lacking. In comparison with their parent drug, the second-generation tetracyclines have a longer elimination half-life and improved bioavailability, and can be taken with food, minimizing gastrointestinal side effects.<sup>56</sup> Second-generation tetracyclines may also achieve beneficial effects for rosacea patients at subantimicrobial dosing. Clinical trials are under way to evaluate subantimicrobial-dose doxycycline hyclate (Periostat, CollaGenex Pharmaceuticals, Inc., Newtown, PA) for the treatment of rosacea.<sup>57</sup> Periostat is indicated for the treatment of adult periodontal disease, with its mechanism attributed to its anticollagenase and antimatrix metalloproteinase properties.<sup>58,59</sup> Preliminary results have shown improvement in some features of rosacea with the use of subantimicrobial-dose doxycycline hyclate (20 mg twice daily), but long-term studies in which its efficacy is compared with that of antimicrobial-dose tetracyclines are required to determine whether subantimicrobial-dose doxycycline hyclate achieves improvement and remission as reliably, as rapidly, and for as long a period. If it were proved effective, its major benefit would be less microbial resistance with long-term therapy. Oral tetracyclines should be avoided in pregnant woman and those contemplating pregnancy.

### Macrolides

Oral erythromycin therapy is employed for rosacea especially when there is intolerance, allergy, or resistance to tetracyclines or when there are contraindications to tetracycline use such as preg-

**Table II.** Cost comparison of various oral antimicrobial therapies used in the treatment of rosacea

Medication	Dose (mg)	Cost*
Tetracycline HCl capsules	250	7.99
	500	7.99
Metronidazole tablets	250	8.86
Flagyl tablets	250	58.99
Erythromycin base (enteric-coated) capsules	250	8.99
Erythromycin base tablets	500	8.15
Minocycline HCl capsules	50	13.99
	100	21.99
Minocin capsules	50	62.99
	100	101.99
Dynacin capsules	50	72.08
	100	127.72
Docyclycline hyclate tablets	100	12.50
Doxycycline monohydrate capsules	50	33.99
	100	45.99
Periostat tablets	20	27.49
Clarithromycin (Biaxin) tablets	250	107.49
Azithromycin (Z-pak) tablets	250	214.95

Source: Drugstore.com online pharmacy (www.drugstore.com); accessed July 15, 2003.

\*Prices, in US dollars, are based on a 30-tablet or -capsule supply.

nancy, lactation, and age younger than 12 years. Erythromycin is in category B for pregnancy.

The second-generation macrolides, clarithromycin and azithromycin, have demonstrated effectiveness for rosacea in recent studies.<sup>60-62</sup> In an 8-week trial, 40 patients underwent treatment with either clarithromycin (250 mg twice daily for 4 weeks, followed by 250 mg once daily for 4 weeks) or doxycycline (100 mg twice daily for 4 weeks, followed by 100 mg once daily for 4 weeks).<sup>60</sup> Clarithromycin achieved significantly faster reductions of erythema ( $P < .005$ ) and papules ( $P < .0005$ ) than doxycycline did at weeks 4 and 6. No significant differences in erythema reduction, telangiectasia, or papule and pustule counts were found between the 2 drugs at week 8. The authors concluded that 6 weeks of clarithromycin therapy was as efficacious as 8 weeks of doxycycline therapy. Clarithromycin also had better tolerability scores during the entire duration of therapy.<sup>60</sup> After 3 years of follow-up, patients who underwent treatment with clarithromycin required the drug 10.2 weeks per year, compared with 14.6 weeks for patients who underwent doxycycline treatment.<sup>61</sup>

Azithromycin was evaluated in 18 rosacea patients, 14 of which completed the 12-week trial.<sup>62</sup> Patients were given oral azithromycin for 12 weeks in decreasing doses. At the end of the trial, there was an 89% decrease in inflammatory lesion scores com-

pared with basal values. Benefits of the second-generation macrolides are improved bioavailability and lack of gastrointestinal side effects in comparison with erythromycin. Controlled clinical trials are necessary to determine the role of second-generation macrolides in both initial and maintenance therapy for rosacea. A cost comparison of the various antimicrobial therapies for rosacea can be found in Table II.

### Metronidazole

Oral metronidazole is an effective alternative for the treatment of rosacea, utilized more often as initial and as long-term rosacea therapy by European practitioners.<sup>9,63-65</sup> In 1976 Pye and Burton reported their experience with 29 patients in whom rosacea was treated with 200 mg of oral metronidazole twice daily. Improvement in papule and pustule counts was significant after 6 weeks of therapy. All of the patients also applied hydrocortisone cream to their faces twice daily. Despite that addition, they noted minimal erythema reduction during the 6-week trial.<sup>9</sup>

In a double-blind, randomized trial, Saihan compared the efficacy of oral metronidazole, 200 mg twice daily, with oxytetracycline, 250 mg twice daily, in 38 patients with papulopustular rosacea. At 6 and 12 weeks, there was no difference between the 2 therapies, but both drugs showed sustained improvement at 12 weeks. Abstinence from alcohol during metronidazole therapy is necessary to avoid alcohol-induced headaches via disulfiram reactions.<sup>63</sup> Although it is relatively safe, metronidazole rarely has been associated with neuropathy<sup>66</sup> and seizures.<sup>67</sup> The drug is well tolerated during pregnancy (category B) and provides an alternative when tetracyclines are prohibited or ineffective.<sup>63,68</sup> A meta-analysis to assess the risk of birth defects while taking metronidazole during the first trimester showed no relationship between metronidazole exposure and congenital malformations.<sup>68</sup>

### Isotretinoin

Multiple small studies from the 1980s established the effectiveness of isotretinoin for rosacea.<sup>69-73</sup> The effects of isotretinoin can be delayed in comparison with standard therapies,<sup>46,74</sup> although a reduction of papule counts may be evident as early as 2 weeks.<sup>70</sup> Irvine, Kumar, and Marks treated erythematotelangiectatic and papulopustular rosacea with either oxytetracycline ( $n = 6$ ; 250 mg twice daily) or isotretinoin ( $n = 5$ ; 30 mg daily) for a 2-month period. All patients had improvement, but the oxytetracycline group had better global assessment scores (reduction of erythema, papules, and pustules) at 8 weeks.<sup>75</sup> Erythema reduction by isotretinoin may have been camouflaged by xerosis and dermatitis

associated with its use. Minimal erythema has been persistent in responsive patients until late into therapy.<sup>70,73</sup>

Although interpretation is limited by their small sample size, Irvine, Kumar, and Marks observed, using a laser-Doppler device (Perimed), that cutaneous blood flow on the cheek, when measured at 25°C and 34°C, was not reduced in patients who underwent oxytetracycline treatment. In contrast, patients in the isotretinoin group showed significantly reduced facial cutaneous blood flow by means of laser-Doppler at both temperatures at 10 weeks.<sup>75</sup> Erdogan et al more recently studied the short-term effects of low-dose isotretinoin in 22 patients with treatment-resistant rosacea. Patients were given 10 mg daily for 4 months. Isotretinoin significantly reduced inflammatory papules, pustules, erythema, and telangiectasia at 9 weeks.<sup>74</sup> Results were further improved at 16 weeks. Ocular lesions regressed at 3 weeks. On the basis of these promising observations, it can be said that larger, more powerful studies are needed to establish the short- and long-term benefits of isotretinoin for rosacea.

Isotretinoin has also been demonstrated to decrease nasal volume in rhinophyma.<sup>70,75</sup> The most significant regression has been noted in younger patients with less advanced disease.<sup>75</sup> Biopsy specimens from phymatous skin prior to isotretinoin therapy showed numerous large sebaceous glands. During isotretinoin therapy, the glands diminished in size and number. Other studies have confirmed the usefulness of isotretinoin for phymatous change.<sup>76,77</sup>

#### MISCELLANEOUS ORAL THERAPIES

In 1971 Spirov, Berova, and Vassilev described the benefits of oral contraceptive monotherapy in 30 women with rosacea.<sup>78</sup> Before therapy they documented "historical and clinical abnormalities of hormonal origin" in 21 of their 30 patients. Complete resolution of papular lesions and improvement of erythema occurred in 18 patients (60%), with maximal effects requiring 4 months of therapy.<sup>78</sup> Mauss treated 3 women with a combination of oral contraceptive plus 10 mg of cyproterone acetate daily between days 5 and 19 of the menstrual cycle. Papules and pustules cleared in each patient by 3 months; however, telangiectasia persisted.<sup>79</sup>

The antiandrogenic effects of spironolactone have also been evaluated for rosacea. Thirteen men with rosacea underwent treatment with a low dose of spironolactone (50 mg daily), and their serum hormone levels were evaluated prior to therapy and 4 weeks into treatment. Two patients discontinued spironolactone treatment owing to malaise. Seven of the remaining patients (63%) had excellent or good

results, including reduction of erythema, papules, pustules, and in some cases telangiectasia.<sup>80</sup> Serum levels of 17  $\alpha$ -hydroxyprogesterone increased significantly after 4 weeks of low-dose spironolactone therapy. Estradiol levels trended upward, but the change was not significant. There were no changes in the levels of testosterone, androstenedione, dihydrotestosterone, and dehydroepiandrosterone sulfate.<sup>80</sup>

Drugs that antagonize flushing are sometimes useful in rosacea refractory to standard therapies. Various medications have met anecdotal success for the management of flushing or erythema in rosacea patients, including  $\beta$ -blockers,<sup>81</sup> clonidine,<sup>82</sup> naloxone,<sup>83</sup> ondansetron,<sup>84</sup> and selective serotonin reuptake inhibitors (personal observation, M.T.P.). In a trial of 24 patients with rosacea, clonidine did not lower mean arterial blood pressure at a dose of 0.05 mg twice daily for 2 weeks, nor did it suppress flushing reactions provoked by hot water, red wine, and chocolate.<sup>82</sup> However, clonidine did lower baseline malar temperature, possibly resulting from a direct or relative peripheral vasoconstrictive effect or from central inhibition of catecholamine release.<sup>82</sup> Nadolol did not prevent spontaneous or laboratory-induced flushing in 15 patients with rosacea.<sup>85</sup> Subcutaneous naloxone was evaluated in a double-blind fashion versus subcutaneous injection of saline solution to determine whether naloxone could prevent alcohol-induced flushing. In 5 of 5 patients, naloxone completely inhibited facial flushing after ingestion of chlorpheniramine followed by beer (6% ethanol).<sup>83</sup> Flushing was not prevented with the saline injections. Evidence supporting the suppression of flushing by other  $\beta$ -blockers is not available.

#### LASER AND LIGHT THERAPIES FOR ROSACEA

Vascular laser therapy for rosacea began in the early 1980s with the argon laser (488-514 nm), initially touted for the treatment of port wine stains and the postrhinoplasty "red nose."<sup>86-89</sup> Over the past 20 years, laser and light therapy for rosacea has evolved to include an ever-increasing number of devices and therapeutic targets. In addition to telangiectasia, the focus for rosacea laser and light therapies now encompasses a broader approach, including the reorganization and remodeling of dystrophic dermal connective tissue and strengthening of the epidermal barrier. Nonablative laser and light are thought to achieve their effects in a variety of ways, possibly including thermally induced fibroblast and endothelial proliferation, or endothelial disruption leading to cytokine, growth factor, and heat shock protein activation.<sup>90</sup>

Laser and light therapy for rosacea is limited by cost; the majority of applications are not covered by medical insurance. Fee schedules vary widely for vascular laser therapy but generally range from \$200 to \$500 per treatment, depending on the surface area treated. Laser therapy can require from 1 to 3 treatments to achieve best results. Treatments are spaced 4 to 8 weeks apart. Intense pulsed light is somewhat more expensive, ranging from \$300 to \$600 per session. Patients may require from 1 to 5 sessions for best results. Intense pulsed light sessions are repeated every 3 weeks.

### Vascular laser therapy

Vascular lasers currently employed for the reduction of telangiectasia and erythema are the standard pulsed dye laser (585 or 595 nm; 0.45 millisecond or 1.5 milliseconds pulse duration), the long-pulsed dye lasers (595 nm, 0.5 to 40 milliseconds), the potassium-titanyl-phosphate lasers (532 nm, 1 to 50 milliseconds), and the diode-pumped frequency-doubled laser (532 nm).<sup>91-94</sup> These short-wavelength lasers emit light that is selectively absorbed by oxyhemoglobin (peak absorptions at 541 nm and 577 nm), leading to vessel destruction without collateral tissue damage according to the principles of selective photothermolysis.<sup>95</sup> Shorter wavelength lasers are best suited for superficial red vessels and persistent erythema. Unlike the argon laser, which sometimes left a groove or atrophic scar along treated vessels,<sup>88,96</sup> posttreatment scarring is a rare occurrence with current vascular lasers.<sup>90,97</sup> Some vascular lasers, especially the pulsed dye laser, are being further studied for their role in dermal collagen remodeling and nonablative rejuvenation.<sup>90,98</sup>

In their 1991 report, Lowe et al treated rosacea in 27 patients with the 585-nm pulsed dye laser. Along with features of persistent erythema and telangiectasia, all of the patients had papules and 19 of 27 patients had pustules. Good or excellent reduction of erythema and telangiectasia was achieved in 24 patients after 1 to 3 laser treatments.<sup>91</sup> Treatments were spaced 6 to 12 weeks apart. No textural or pigmentary adverse reactions occurred. Fourteen patients were able to reduce the dosage of their antibiotic maintenance regimen subsequent to laser therapy.<sup>91</sup> The KTP laser was found to be moderately effective for the treatment of facial telangiectasia in 47 patients with rosacea.<sup>99</sup> In 38% of patients, one KTP treatment achieved a 70% or greater reduction of telangiectasia. Two treatments were required in 32% of the patients to achieve the same result.<sup>99</sup>

West and Alster compared the long-pulsed dye laser with the KTP laser in 8 patients with facial telangiectasia. In each patient, one area of telangi-

ectasia was treated with the long-pulsed dye laser (15 J/cm<sup>2</sup>, 1.5 millisecond, 2 × 7 mm handpiece) and the other with the KTP laser (15 J/cm<sup>2</sup>, 10 milliseconds, 1-mm handpiece). The percentage of vessel clearance was greater for the long-pulsed dye laser ( $P < .05$ ); however, the KTP laser caused less pain, no purpura or crusting, and minimal posttreatment erythema.<sup>92</sup> Hyperpigmentation was the most common side effect of long-pulsed dye laser therapy, present in 5 of 7 patients after one treatment and persisting at 12 weeks. In all patients, hyperpigmentation was resolved at 24 weeks. The long-pulsed dye laser has the advantage of treating larger and deeper vessels. Short pulse durations induce greater tissue trauma, which results in purpura. Longer pulses deliver equivalent energy at a slower rate to heat vessels uniformly and gently, minimizing post-treatment purpura while allowing the treatment of larger vessels. In addition, purpura, as well as edema and pain, can be minimized with the concomitant use of epidermal cooling sprays and gels.

Deeper facial vessels require longer wavelength lasers for eradication. Because hemoglobin is also absorbed around 800 nm and above 1,000 nm, the diode laser (810 nm, 1 to 1000 milliseconds), the long-pulsed Alexandrite laser (755 nm; 3, 5, 10, 20 milliseconds), and the long-pulsed neodymium: yttrium-aluminum-garnet laser (1,064 nm, 1 to 100 milliseconds) can be effective options for larger and deeper blue vessels.

### Intense pulsed-light therapy

Intense pulsed light is multichromatic, noncoherent light of multiple wavelengths from yellow to infrared. Filters are utilized to establish the short end of the spectrum, which usually begins between 550 and 600 nm. The high end of the spectrum ranges up to 1,400 nm. Intense pulsed light penetrates the skin deeper than vascular lasers and targets multiple chromophores and varying depths, including melanin and hemoglobin. In addition to the treatment of vascular lesions, pigmented lesions, photoaging, and unwanted hair,<sup>100-105</sup> intense pulsed light has shown promise for nonablative facial rejuvenation.<sup>90,106-110</sup> The mechanism for nonablative rejuvenation may be light-induced cytokine activation and growth factor release, which contribute to dermal collagen, vascular, and elastic tissue remodeling.<sup>90</sup> The benefits of intense pulsed light include a larger spot size to treat larger areas, the ability to treat larger and deeper vessels, and its promotion of dermal collagen remodeling.<sup>107</sup>

Photoderm VL (Lumenis, Santa Clara, Calif) was approved by the FDA for the treatment of facial telangiectasia in 1995. Multiple models of intense



pulsed light therapy have followed, with reported success in thousands of patients with vascular lesions and a low incidence of side effects.<sup>99,110-115</sup> Intense pulsed light therapy was successful anecdotally in the treatment of chronic facial erythema in a 33-year-old woman with systemic lupus erythematosus and rosacea.<sup>116</sup> The treatment did not exacerbate her lupus. Clearance of her erythema required 2 treatments, and improvement was maintained at 1 year with no adverse effects.<sup>116</sup>

Angermeier treated facial vascular lesions in 200 patients (including 74 patients with rosacea) with intense pulsed light (PhotoDerm VL). Of 188 patients examined at follow-up, 174 (92.5%) had 75% to 100% clearance of their lesions.<sup>111</sup> Three patients with rosacea required only 1 treatment for complete clearance; however, most required at least 2 treatments. Side effects other than transient erythema and edema occurred in 34 cases and included bruising, edema lasting longer than 48 hours, transient hypopigmentation (resolved at 4 months), and 1 case of conjunctival injection. Weiss, Weiss, and Beasley evaluated their long-term clinical results several years after intense pulsed light therapy. At 4 years, telangiectasia was improved in 82%. Facial skin had the greatest long-term improvement, with the maintenance of improved texture in 90% of patients, reduced telangiectasia, and more uniform pigmentation. The chest skin maintained improvement in 76%, and the neck in 71%. The authors concluded that 4 of 5 patients benefited over the long-term.<sup>107</sup>

### **ROSACEA MANAGEMENT: A SUBTYPE-DIRECTED APPROACH**

On the basis of their clinical and histologic variations, it is no surprise that erythematotelangiectatic, papulopustular, phymatous, and glandular rosacea respond to different therapies. From a practical standpoint, subtyping can guide choice and structuring of therapy. Certain modalities will be useful in all patients, stemming from overlap among the subtypes; however, the timing of their use may vary. For example, to the extent that all rosacea patients suffer from some degree of central facial redness, intense pulsed light or vascular laser therapy may be useful at a certain point in all subtypes.

The following are interventional strategies utilized by the authors for the treatment of rosacea; they have been guided and supported by the data presented herein. Studies to establish the efficacy of these combinations in each rosacea subtype are needed. While the approach to treatment of each subtype differs, the strategies designed to repair and prevent structural disorganization in the dermis can be ap-

plied to all patients. Therapy that is common to each subtype is discussed first, followed by subtype-specific interventions.

### **Prevention and repair**

Most rosacea patients display some degree of solar damage. The principles of sun avoidance and sun-screen choice in this population have been discussed. Patients should understand that the addition of these practices is preventive. Likewise, avoiding trigger factors is an important preventive mechanism. Patients should be educated about known triggers, and their own triggers should be identified and avoided if feasible. Finally, nonirritating cosmetics may be recommended for the purpose of concealing the signs and symptoms of rosacea in appropriate patients (Table I).

Standard medical therapies for rosacea have focused mainly on minimizing inflammation. Only recently has the repair of vascular and connective tissue disorganization become a target of rosacea therapeutics. Dermal connective tissue repair and reorganization have been demonstrated after certain laser and light therapies.<sup>112,113</sup> Small cohorts of rosacea patients have undergone treatment with intense pulsed light and have had decreased erythema and telangiectasia and in some cases normalization of their flush response.<sup>114,115</sup>

Topical retinoids represent one medical therapy capable of reorganizing dermal collagen and blood vessels, while also providing an anti-inflammatory effect.<sup>42,43,46,116-120</sup> While it is clear that studies are required to establish the efficacy of this approach for rosacea, one author (M.T.P.) has been utilizing a topical retinoid approach adjunctively for rosacea for 5 years. To avoid irritation, patients protect their facial skin with an oil-in-water barrier emollient just prior to the application of the topical retinoid. Patients apply 0.025% tretinoin initially to ensure tolerance (dose limited to "one pea-sized drop" to the entire face before bedtime). Tretinoin strengths are gradually increased to 0.05% and 0.1% formulations. After 1 year, application can be decreased to 2 to 5 nights per week. Continued sun avoidance and protection must be stressed. Use of the barrier emollient can also be reduced, depending on ambient temperature, humidity, and patient tolerance.

On the basis of personal observations (M.T.P.), rosacea patients note improvement in their skin texture after 1 month of therapy with a barrier emollient plus tretinoin. After 1 year of therapy, patients have developed normal (physiologic) flush responses and little or no background erythema (M.T.P.). Papular flares and the need for oral tetracyclines are uncommon. Randomized, controlled

clinical trials and histologic studies have not been performed to substantiate these clinical observations. Similar clinical results can be achieved with low-dose oral isotretinoin therapy.<sup>46,74</sup> The mechanism by which retinoids could influence neurologically mediated flush responses is unknown. It is possible that dermal “remodeling” better equips rosacea-affected skin for the clearance of edema and erythema associated with flushing.

### **Erythematotelangiectatic subtype**

Erythematotelangiectatic rosacea patients most often have barrier disruption and sensitivity to topical products. Education about cosmetic and sunscreen choices is of great importance. In those patients with minimal barrier dysfunction, one or a combination of a gentle, topical anti-inflammatory product such as metronidazole or sodium sulfacetamide–sulfur may be applied in the morning and followed by sunscreen. Evening application of barrier emollient and tretinoin may be started concomitantly.

If irritant reactions are a prominent part of the history of an erythematotelangiectatic rosacea patient, or if scaling and bright erythema are present, a physical sunscreen and a barrier-protective emollient twice daily while commencing oral antibiotics may be beneficial. Once the cutaneous sensitivity is lessened, the therapy outlined above may be initiated. Alternatively, barrier protection, along with isotretinoin in doses of 10 to 20 mg daily for 3 to 4 months, may lessen flushing episodes and erythema in some patients, allowing for the institution of topical medical therapy (personal observation, M.T.P.).

Occasionally, in patients with severe irritant responses to all products, one of the authors will utilize *1 week only* of a twice-daily application of a high-potency steroid ointment, followed by 1 week of this ointment once daily and tacrolimus ointment once daily, followed by tacrolimus ointment twice daily until the irritation decreases (personal observation, W.D.J.). This is combined with oral minocycline. After 1 to 2 months, this regimen will then allow institution of other topical medical treatments, as mentioned above. In erythematotelangiectatic rosacea patients who prefer a surgical approach and can afford intense pulsed light or laser interventions, these treatments may be selected as first-time therapy.

### **Papulopustular subtype**

Initial therapy to establish control of the disease (typically lasting 2 to 3 months) usually requires the combination of oral and topical antimicrobial agents.

Rapid control can be achieved with 1 to 3 months of oral antimicrobial therapy, while one or more topical antimicrobials (or tretinoin) are begun concomitantly. Skin sensitivity is less common in papulopustular rosacea, so all topical therapeutic options are well tolerated in at least half of the cases, including benzoyl peroxide or benzoyl peroxide–topical antibiotic combination formulations. Isotretinoin is rarely needed for the papulopustular rosacea subset. Disease in these patients usually is controlled easily with oral tetracyclines and topical antimicrobials. To minimize the number of new medications that the patient must manage, topical tretinoin is often not added to the initial therapy for papulopustular rosacea.

Long-term management of papulopustular rosacea often comprises the use of topical agents only. An effective combination topical regimen might include metronidazole, sodium sulfacetamide–sulfur, azelaic acid, or benzoyl peroxide followed by sunscreen each morning. In the evening, a protective emollient, followed by tretinoin cream, may be applied. Vascular lasers and intense pulsed light are adjunctive options for the treatment of erythema and telangiectasia. Intense pulsed light may also limit flushing episodes, but more data are needed in this regard.

### **Glandular rosacea**

Glandular rosacea (see part I, *J Am Acad Dermatol* 2004;51:327-41) patients often have a history of acne vulgaris and may have overlap of acne with their rosacea. They have good responses to topical antimicrobials. Benzoyl peroxide and benzoyl peroxide–antibiotic combination formulations tend to work quickly and are well tolerated in these patients. Along with the topical regimen, oral tetracyclines are important to establish initial control of papules and pustules. Oral therapy generally is continued for 1 to 3 months. Most glandular rosacea patients do not have the development of telangiectasia; however, they may have a component of flushing. In mild to moderate glandular rosacea, topical retinoids can be added to topical or oral antimicrobial therapy as part of initial management. Severe inflammatory or nodulocystic disease can be controlled initially with isotretinoin, which should be followed with long-term management with topical tretinoin.

Females with glandular rosacea often complain of increased sebum production, large pore size, and thickened skin. They may also present with a predominantly “lower-face” or perioral distribution of papules and pustules. In such cases, spironolactone in low doses (25 to 50 mg daily) or oral contraceptive pills, or both, may prove helpful. Isotretinoin is also

effective for minimizing sebum production in the short term.

### Phymatous subtype

Isotretinoin monotherapy is beneficial for early to moderate phymatous rosacea. Advanced phyma should be treated with surgical therapy or the combination of surgery followed by isotretinoin therapy. Surgical approaches to the reshaping of rhinophyma have included the use of a heated scalpel, electrocautery, dermabrasion, laser ablation, tangential excision combined with scissor sculpturing, and radiofrequency electrosurgery. Often a combination of these approaches is used to obtain the best aesthetic result.<sup>76,117,118</sup>

### FUTURE STUDIES

Few questions regarding rosacea pathogenesis have been sufficiently answered, and many more remain uninvestigated. The identification of genetic factors and gene loci that predispose affected persons to a rosacea phenotype is now under way. It is clear that certain populations are more commonly affected by rosacea, and as many as 40% of patients with rosacea have a relative affected with rosacea.<sup>42</sup>

One area that requires investigation is the histologic and pathologic basis of papules and pustules, whether they are follicle-based or not, and whether microorganisms play a role in their development, considering the therapeutic responsiveness of papules and pustules to benzoyl peroxide, an agent with no anti-inflammatory properties. Further, it is not clear whether the dermal vasculature and lymphatics play a primary or secondary role in rosacea. Soybe's technique of facial massage should be investigated to assess whether it reduces central facial edema, inflammatory lesions, and erythema. A most important advance will be the determination of how and where the skin barrier is altered in certain rosacea-affected persons, and how barrier dysfunction may modify the subtype manifested. Furthermore, what role does the vehicle play in rosacea therapeutics?

Elucidating the neurologic or hormonal mechanisms that generate flushing in rosacea might help to determine agents that counteract flushing and minimize flaring. Hormonal influences may account for the differing predilection for phyma in men versus women. Hormonal factors seem to play a role in the tendency for menopause-associated flushing to induce or flare rosacea (and they seem to promote or exacerbate migraine headaches in the same population). The role of the sebaceous gland and other hormonally modified features of rosacea are

far from understood. Anecdotal success of spironolactone for glandular rosacea requires further study, as this drug may allow better control of sebaceous function and phyma in predisposed persons. Isotretinoin dramatically affects sebaceous function, but this effect does not account for improvements seen in all isotretinoin-responsive rosacea patients. Isotretinoin may possess the ability to modify facial blood flow, and this aspect should be carefully investigated in controlled trials.

Insight regarding the role of ultraviolet light exposure and photodamage in rosacea-prone persons is long overdue. An expanding area of rosacea research involves the induction of vascular endothelial growth factor, prostaglandins, and cytokines by ultraviolet light. Tetracycline is known to modulate arachidonic acid metabolism, Cyclooxygenase enzymes, and prostaglandin production in vitro. Retinoids also modulate the expression of the Cyclooxygenase-2 gene and prostaglandin synthesis. These areas will be the focus of future research surrounding the question of ultraviolet light and its effects in rosacea.

Long-term studies that compare laser and light modalities and their specific treatment protocols are necessary, not only to maximize therapeutic outcomes but also to determine whether dermal and vascular remodeling and the reversal of photodamage generate lasting remissions. Likewise, can retinoids, via the reversal of photodamage or anti-inflammatory mechanisms, achieve remissions in rosacea symptomatology? Certainly more questions than these remain. We hope that investigation has been stimulated and that important progress will follow.

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## Answers to CME examination

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| 10. d | 25. F |
| 11. c | 26. T |
| 12. e | 27. T |
| 13. c | 28. T |
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