Rosacea: I. Etiology, pathogenesis, and subtype classification

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Rosacea is one of the most common conditions dermatologists treat. Rosacea is most often characterized by transient or persistent central facial erythema, visible blood vessels, and often papules and pustules. Based on patterns of physical findings, rosacea can be classified into 4 broad subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. The cause of rosacea remains somewhat of a mystery. Several hypotheses have been documented in the literature and include potential roles for vascular abnormalities, dermal matrix degeneration, environmental factors, and microorganisms such as *Demodex folliculorum* and *Helicobacter pylori*. This article reviews the current literature on rosacea with emphasis placed on the new classification system and the main pathogenic theories. (J Am Acad Dermatol 2004;51:327-41.)

Learning objective: At the conclusion of this learning activity, participants should be acquainted with rosacea's defining characteristics, the new subtype classification system, and the main theories on pathogenesis.

Rosacea is a common condition characterized by transient or persistent central facial erythema, visible blood vessels, and often papules and pustules. Because the facial skin is the predominant site of involvement, many patients sense that rosacea alters their social and professional interactions, leading to problems on the job, in their marriage, or in meeting new people. These common issues have led to the formation of a large active patient advocacy group, the National Rosacea Society, which produces newsletters, encourages research by offering grants, and distributes educational and supportive materials to professionals and patients.

While therapeutic interventions are expanding with new light-producing devices and topical remedies, our understanding of the pathophysiology of rosacea has not progressed substantially. New treatments target empirically the signs and symptoms without understanding the mechanism by which these pathologic processes take place. It is possible that with renewed interest, funding sources, and advanced technology, more and better studies to discover the pathogenesis of rosacea will follow. However, research into a disease state requires precise definitions and exclusion, and many of the studies performed so far have been hampered by a lack of such disease-defining terms. Complicating the acceptance of any comprehensive set of diagnostic criteria is the fact that there is no benchmark laboratory test and that patients with rosacea demonstrate a broad spectrum of possible findings. There has been recognition that some patients' clinical pictures are dominated by a certain set of findings, such as redness and flushing (erythematotelangiectatic rosacea [ETR]), and others' by papules and pustules (papulopustular rosacea [PPR]). A few studies segregate their patients into these 2 subtypes and have shown divergent results of the factors investigated. A recent article has helped to better define and subclassify rosacea into 4 main nosologic subtypes.[1] What follows is a review of the literature about the pathophysiology of and the treatment options for rosacea in the context of these recently designated subtypes.

DEFINITION AND SUBTYPES

The April 2002 issue of this Journal contained an important article in which members of an expert committee assembled by the National Rosacea

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Society reported their conclusions of a meeting designed to standardize diagnostic criteria for rosacea.[1] The defining characteristics are a loosely associated series of signs and symptoms. The presence of flushing, persistent erythema, telangiectasia, papules, and pustules in a central facial distribution is certainly enough to allow even dermatologic neophytes to recognize the common classic cases; however, this imprecise clustering of findings does not adequately set a standard on which future studies of rosacea should be based. One reason for a lack of precision may be the desire to account for those patients whose condition lies apart from the center of the classic disease spectrum, of which there are a wide variety of examples.

Rosacea is a disease, however, for which there is no laboratory benchmark test and for which we are many years from understanding the basic pathophysiology and etiopathogenesis. Therefore we currently need to explicitly and meticulously define the condition on the basis of recognizable morphologic characteristics. The difficulty in interpreting data from the large body of literature amassed to date is to some degree a result of such lack of precision in the past.

The expert panel recognized 4 subtypes of rosacea. The concept that patients present with a preponderance of one or a clustering of signs is most useful. Dermatologists know that some patients have only persistent erythematous cheeks without papules and pustules. These patients often are the same ones who have dramatic histories of flushing to a wide variety of stimuli, who bitterly complain of burning and stinging, and who often are intolerant of topically applied products. Contrast such patients with the sebaceous-skinned man with many papules, pustules, and even nodular erythematous lesions, and a background of central facial erythema. Patients like him are often not "flushers and blushers," have fewer, if any, symptoms of burning and stinging, and tolerate topical medications better than patients with ETR.[2]

These 2 classic subtypes require different therapeutic approaches. Findings of studies of the pilosebaceous apparatus, cutaneous sensitivity, sun-induced inflammatory processes, or many other variables would also be predicted to be quite diverse between such groups. In experimental studies, the lumping of patients with various clinical presentations may mask insights into rosacea.

Finally, rosacea has been historically divided into stages. It is often stated or implied that stages of the disease evolve from one to another.[3-6] The committee did not discuss stages and recognized only one variant.[1] This advance in the classification and definition of disease will certainly aid in lessening the confusion in future research and publications about this subject.

DISEASE DEFINITION

The expert committee stated that the diagnosis of rosacea requires the presence of one or more of the following primary features concentrated on the convex areas of the face: flushing (transient erythema), nontransient erythema, papules and pustules, and telangiectasia.[1] While we agree with the basic diagnostic criteria presented, we believe that additional refinements are needed. For instance, is a history of flushing in a central facial distribution enough to define rosacea? How long is the *transient* erythema of the flush? Are facial papules and pustules in a central facial distribution characteristic enough to define rosacea? How long does the nontransient erythema persist? We believe that the most important finding is persistent erythema of the central portion of the face lasting for at least 3 months. There is a marked tendency to spare the periocular skin. We propose this type of erythema to be the sole requisite criterion for the diagnosis of rosacea. Flushing, papules, pustules, and telangiectases on the convex surfaces are supportive characteristic findings, but not necessary for diagnosis.

Secondary features include burning or stinging, edema, plaques, a dry appearance, ocular manifestations, perpheral locations, and phymatous changes.[1] When present, the relative abundance of these associated findings will dictate the subtype of disease the patient manifests. As will be discussed in the next section, subtype designation is of paramount importance because the therapeutic implications are quite different among the subtypes.

Several diseases must not be present: polycythemia vera, connective tissue diseases (lupus erythematosus, dermatomyositis, and mixed connective tissue disease), carcinoid, and mastocytosis. Patients who have applied topical steroids to the central facial convexities over a long period are also excluded. Rosacea primarily affects the face, so the presence of extrafacial erythema is generally an exclusionary sign, with the exception of sites described under each subtype.

A myriad of diseases that cause a red facial appearance usually are not difficult to discern from rosacea. Most will fall aside when limitation to specific sites of the face and chronicity are specified. Patients with polycythemia vera, connective tissue disease, carcinoid, or mastocytosis will generally manifest a variety of systemic symptoms and extrafacial signs that will lead to the appropriate diagnosis. These

conditions also have specific laboratory markers that will confirm the clinical suspicion.

Finally, photosensitivity and allergic contact dermatitis will at times be considerations. The former will usually affect other sun-exposed sites, such as the dorsal part of the hands, ears, and neck; phototesting is the diagnostic test. Allergic contact dermatitis is itchy, scaly when present for a long period, and often present either intermittently or at other sites as well. Patch testing should be employed as a diagnostic test when itch is a prominent symptom or when allergy to a topical product occurs as a complication of rosacea treatment.

ROSACEA SUBTYPES

It is of paramount importance to indicate the subtype of rosacea that is diagnosed, as there is a wide spectrum of patients for whom the umbrella term *rosacea* is commonly rendered. The classic patient at the midpoint of the spectrum—Wilkin's typological center—is easily recognized.[5] It is likely that this epicenter was what originally separated rosacea most easily from other diseases. However, manifestations of rosacea are protean, involve multiple associated signs and symptoms, and are often modified by therapeutic intervention. Consequently, the red-faced patients who present to the dermatologist with manifestations outside this "nodal center" comprise a large portion of the patients currently being studied and designated as having rosacea.

The simple diagnosis of rosacea without the appended subtype may be viewed as akin to the diagnosis of alopecia without the appropriate designator. Certainly alopecia areata differs in presentation, pathophysiology, and therapeutic options from androgenetic alopecia. Likewise, the patient with sebaceous, thickened skin whose face is dull red and studded with papules, pustules, and nodulocystic lesions is quite different from the thin-skinned bright pink-faced patient who complains bitterly of burning and stinging. We believe the difference is likely to be reflective of varying pathophysiologic mechanisms also. Certainly these divergent conditions require alternate therapeutic approaches, as suggested by Dahl in the differential treatment recommendations for pustules versus telangiectases.[7]

Some authors have theorized that rosacea progresses from one stage to another.[3-6] The expert committee's recent report did not include this notion.[1] A progression from one subtype to another probably does not take place, except perhaps in the cases of severe papulopustular or glandular rosacea that eventuate into phymatous forms.

Erythematotelangiectatic type (ETR)

The flushing that rosacea patients experience is prolonged. Many people without rosacea experience evanescent flushing in response to embarrassment, exercise, or hot environments.[8] The flushing of rosacea, however, is not the evanescent several seconds to few minutes of pinkness that is commonly experienced. Usually rosacea patients describe their flushing to last longer than 10 minutes. Such a prolonged vasomotor reaction may help in differentiating physiologic flushing from that seen in rosacea patients. The central portion of the face is generally the site of the most intense color,[9] but the redness may also involve the peripheral portion of the face, the ears, the neck, or the upper part of the chest.[10] There is characteristic sparing of the periocular skin. The stimuli that bring on such flushing may be acutely felt emotional stress, hot drinks,[11] alcohol,[12] spicy foods,[8] exercise, cold or hot weather, or hot baths or showers.[13] At times the episodes are without known stimuli. Often a burning or stinging sensation accompanies the flush of rosacea; however, sweating, light-headedness, or palpitations do not.

Patients with ETR (Fig 1) have a lower threshold for irritation from topically applied substances.[2] They experience stinging and burning that can be quite severe. Topically applied products may exacerbate these symptoms. They describe itch in response to sunscreens, cosmetics, and medicaments meant to alleviate the redness. Patients in whom itch is a prominent symptom deserve patch testing. Those who complain of acute sun-induced symptoms likewise deserve phototesting and photopatch testing; however, results usually prove negative. The skin is usually fine in texture without a sebaceous quality or oiliness that better characterizes the other subtypes. At times roughness and scaling are seen in the affected sites, probably reflecting a chronic, low-grade dermatitis.[7] There is usually no history of acne.[4]

Papulopustular rosacea (PPR)

Patients with PPR (also known as classic rosacea, pink papular rosacea, and typologic center disease) present with a strikingly red central portion of the face but have persistent or episodic inflammation characterized by small papules that may be surmounted by pinpoint pustules (Fig 2). Edema may accompany such episodes but is frequently subtle in its expression.[14,15] There is almost universal sparing of the periocular skin, which contrasts strikingly with the intense redness at adjacent sites. A history of flushing is often present; however, this symptom is usually milder than that experienced in

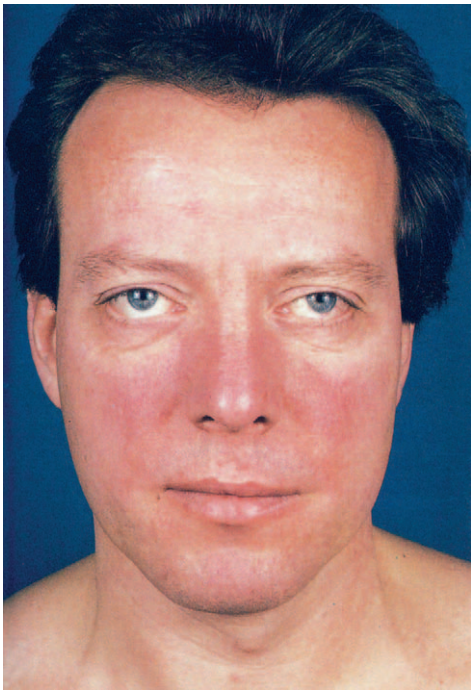

Fig 1. Erythematotelangiectatic subtype. (From Plewig G, Kligman AM. Acne and rosacea, 3rd ed. Berlin: Springer-Verlag, 2000. p. 471; used with permission.)

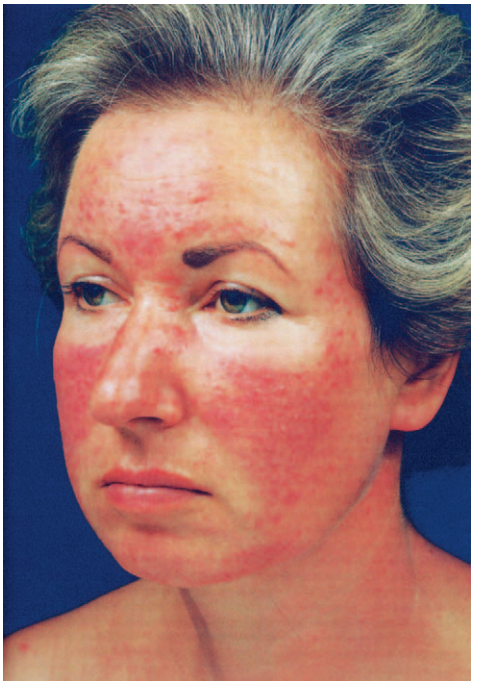

Fig 2. Papulopustular subtype. Central facial redness, circumoral and circumocular sparing, and small erythematous papules, some of which are topped with a small pustule. (From Plewig G, Kligman AM. Acne and rosacea. 3rd ed. Berlin: Springer-Verlag; 2000. p. 469. Reprinted with permission.)

patients with ETR. Irritation from external stimuli is also not as constant a feature[2]; thus scaling and roughness are often absent. These patients are most often women in midlife.[4] Telangiectases are often subtly present but may be obscured by the generally erythematous background.

The episodes of inflammation may lead to chronic edema. The presence of the more dramatic manifestation of solid facial edema and phymatous changes can occur in men with this subtype of disease but are distinctly rare in women.[16,17] The reasons these problems tend to be less common in women are unknown but may relate to hormonal influences, earlier therapy that prevents repeated insults, or other, unknown factors.

Phymatous rosacea

The expert committee designated phymatous rosacea as one of the 4 rosacea subtypes.[1] Phymata include marked skin thickening and irregular surface nodularities, and can occur on the nose (rhinophyma; Fig 3), chin (gnathophyma), forehead (metophyma), one or both ears (otophyma), and eyelids (blepharophyma).[18] Four variants of rhinophyma (glandular, fibrous, fibroangiomatous, actinic) can be recognized clinically and have distinct histopathologic features.[18]

The discussion of phymata in the context of writings about rosacea is not preceded by suppositions that it is a vascularly based or a sun-induced condition, as other manifestations of rosacea are.[7,18-20] In parallel with different subtype-targeted therapies, phymata are approached in a dramatically different fashion from the other subtypes of rosacea. The mainstays of therapy are isotretinoin and surgical correction.[18,20-25]

Ocular rosacea

Blepharitis and conjunctivitis are the most common findings in rosacea patients with ocular manifestations (Fig 4).[14,26-28] Inflammation of the lids with recurrent chalazion and inflammation of the meibomian glands may be present. Interpalpebral conjunctival hyperemia, conjunctival telangiectases, and watery or dry, irritated eyes can occur. Burning or stinging, itching, light sensitivity, and a foreign body sensation are frequent symptoms in the patient with ocular rosacea. Keratitis, scleritis, iritis, and complications of such involvement are infrequent but can occur.[14,26,27,29-35]

Ocular rosacea may precede the cutaneous signs by many years[36]; however, in most dermatology

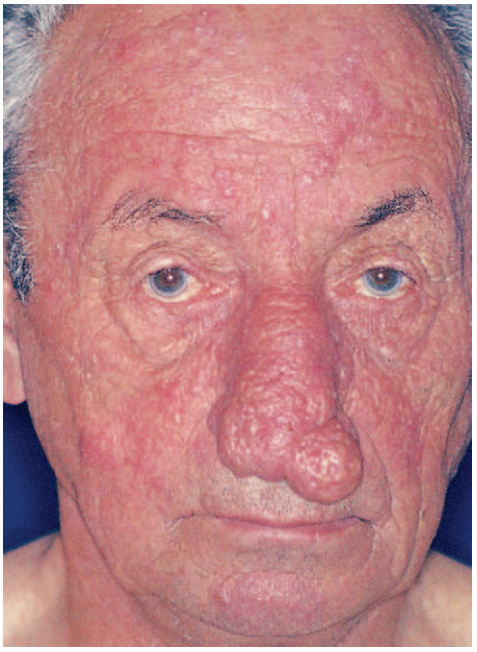

Fig 3. Phymatous rosacea. Thick sebaceous skin, papules and pustules, marked skin thickening, and irregular surface nodularities most prominent on the nose. (From Plewig G, Kligman AM. Acne and rosacea. 3rd ed. Berlin: Springer-Verlag; 2000. p. 475. Reprinted with permission.)

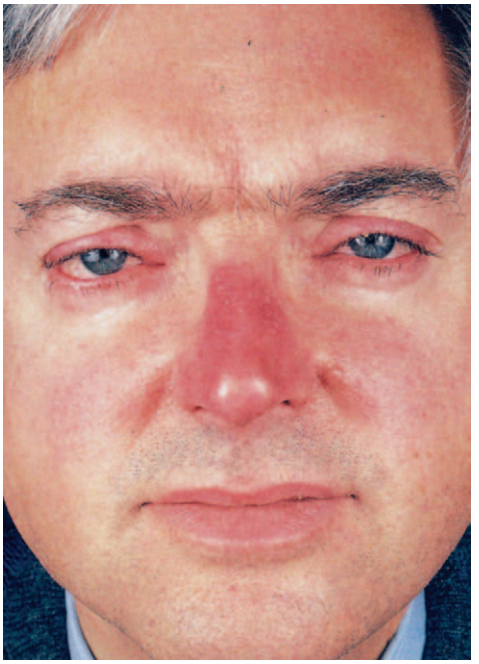

Fig 4. Ocular rosacea. Erythema of the nose is most prominent. Associated conjunctivitis and blepharitis are demonstrated. (From Plewig G, Kligman AM. Acne and rosacea. 3rd ed. Berlin: Springer-Verlag; 2000. p. 481. Reprinted with permission.)

practices, concurrent presentation or eye findings following the skin signs are more often observed.[26,27] As discussed below, distinct therapies for ocular manifestations make it extremely important for dermatologists to actively pursue a history of eye complaints and to conduct a thorough examination of the lid margins and conjunctiva.

OTHER CLINICAL CONSIDERATIONS

Glandular rosacea

One phenotype displayed in certain rosacea patients is quite different from the other 4 classic subtypes recognized above. We propose the term *glandular rosacea* (GR) to describe this phenotype, which is commonly seen and illustrated in textbooks (Figs 5 and 6) but has not previously been clearly separated into a distinct nosologic subtype. GR is most common in men who have thick, sebaceous skin. Edematous papules and independent pustules are often of large size, and nodulocystic lesions may be present. These lesions often will cluster in the central and inner aspects of the cheeks but may be seen in any sites that show erythema. In women with this subtype, the chin is often a more favored location. Frequently such patients will have a history of adolescent acne with the typical scars. Unlike ETR and PPR, there is usually an absence of sensitivity to and complaints of burning and stinging from topical agents. Therapeutic options, then, are extended to include benzoyl peroxide and benzoyl peroxide–antibiotic combinations, which are frequently dramatically effective.

The marked periocular sparing is again notable. Flushing is less frequently present than in the other subtypes. The background redness is less dramatically pink but instead will frequently have shades of rust. The hue surrounding the raised inflammatory lesions, however, will be brightly erythematous, and the edema surrounding them is often dramatic. The dermal effects of chronic sun damage and the dilated vasculature may be less visible because of the overlying hypertrophied sebaceous glands. The patient may exhibit chronic central facial edema if the process has been allowed to continue untreated or if particularly dramatic episodes of nodulocystic disease have occurred. A predisposition to the development of rhinophyma is present.

Extrafacial lesions

When discussing rosacea, many experts will relate that extrafacial lesions are sometimes seen.[10,37,38] In the erythematotelangiectatic form, one may observe

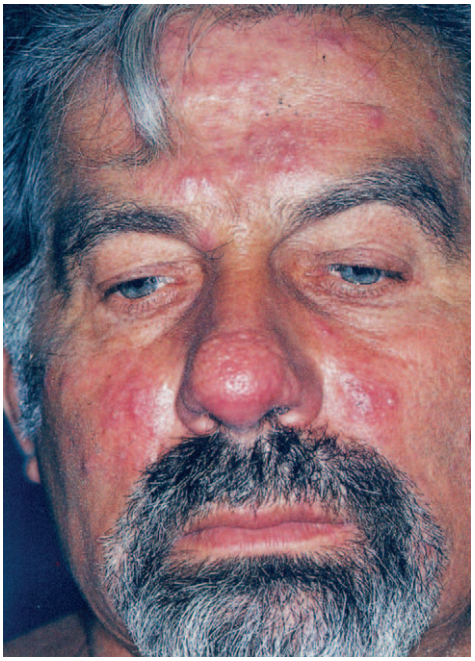

Fig 5. Glandular subtype. Central facial erythema, papules and pustules associated with large-pored seborrheic skin. (From Plewig G, Kligman AM. Acne and rosacea. 3rd ed. Berlin: Springer-Verlag; 2000. p. 471. Reprinted with permission.)

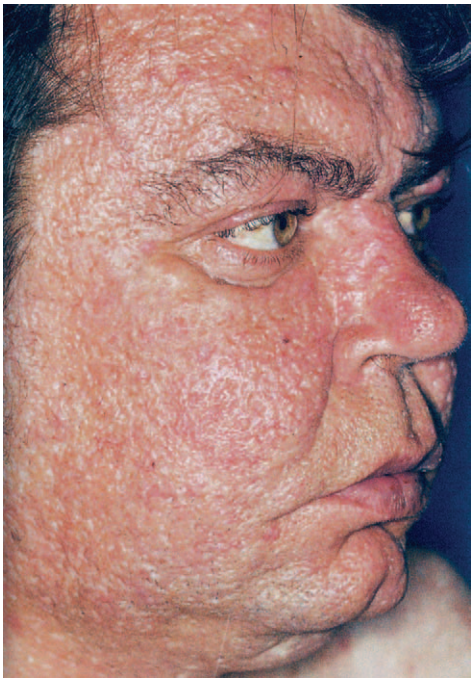

Fig 6. Glandular subtype. Central facial erythema, diffuse sebaceous gland hyperplasia and prominent pores. (From Plewig G, Kligman AM. Acne and rosacea. 3rd ed. Berlin: Springer-Verlag; 2000. p. 475. Reprinted with permission.)

macular redness of the ears, lateral facial contours, neck, upper portion of the chest, and scalp. These extrafacial manifestations in ETR patients are uncommon and are usually seen only in areas affected by flushing and chronic sun damage.[39] Acneiform lesions have been reported to occur on the central part of the chest, the scalp, the neck, and occasionally the limbs.[4,10,38,40,41] Further characterization of the erythematous papules and pustules and nodulocystic lesions in these patients should lend insight into the nature of these uncommon extrafacial lesions. Finally, the red scrotum syndrome—characterized by intense redness, burning, and stinging[42]—has been hypothesized by some to be a manifestation of rosacea. In the many patients with the red scrotum syndrome seen by the authors, none had recurrent flushing of the scrotum, only occasionally has facial rosacea been present, and in none did therapy utilized in the treatment of rosacea result in improvement of the scrotal manifestations. Conversely, after questioning hundreds of patients who presented for treatment of rosacea, the authors have not found anyone with burning and stinging of the scrotum. This finding is in contrast to the frequent discovery of unrevealed eye symptoms on specific questioning. In our opinion, the red scrotum syndrome is the result of chronic irritation, long-term steroid use, or atopic dermatitis (personal observations, W. D. J., M. T. P., G. H. C.).

Sun damage

Sun damage is a mildly inflammatory process and can produce variably conspicuous telangiectases and erythema. These findings are present on the entire sun-exposed surfaces; hence, while they spare the periocular skin as in rosacea, they also affect the periphery of the face, the neck (sparing the area below the chin), the upper part of the chest (particularly in women), and the dorsal portions of the ears (in patients with short hair). In addition, dyspigmentation is present to some degree in most patients.

It is not uncommon for patients who present for treatment of rosacea to have only severe sun damage. These same patients may have joined national societies for the condition, be avoiding triggers publicized to induce flushing (even without episodes of flushing), and be concerned about the eventual development of a "W. C. Fields nose." It is important to differentiate such patients from those with rosacea. Patients with solely actinic changes should be directed to appropriate preventive and corrective strategies, such as the daily use of sunscreens and sun-avoidance measures. While some overlapping of

treatment strategies exists, there is of course no need to incur lifestyle changes in diet and exercise or to fear the enlarged, bulbous nose of rosacea in the patient with solely sun-damaged skin.

Topical steroid use

The prolonged use of topical steroids may reproduce many of the signs and symptoms characteristic of PPR.[43,44] It is thought that anyone may develop this complication; however, it may be that rosacea-prone persons are more susceptible.[45,46] The condition is not necessarily limited to the central part of the face but rather occurs in the facial sites where the steroids are applied. It is not considered to be a subtype of disease but rather an adverse drug effect that mimics rosacea. The best treatment for this *steroid-induced rosacea-like eruption* requires not only stopping the medication but also intervening with antibiotics and topical tacrolimus.[47,48] This latter agent is not known to be effective in rosacea but may help calm the symptomatic dermatitis seen in ETR (personal observations, W. D. J., G. H. C., M. T. P.).

Perioral dermatitis

Perioral dermatitis has often been classified within the umbrella of rosacea variants. However, the distribution, signs, and symptoms vary from the definitions presented. Consequently, despite responding to agents normally effective for rosacea, it is not included as a subtype of rosacea.[1]

Granulomatous lesions

Granulomatous rosacea was classified by the expert committee as a disease variant characterized by periorificial yellow, brown, or red monomorphic papules or nodules that, when severe, can lead to scarring.[1] While it is true that most experienced physicians may accurately predict clinical lesions that will at biopsy show granulomatous inflammation, the term *granuloma* is a histologically, not clinically, defined term. Patients with "granulomatous rosacea" often do not have persistent facial erythema, may not have disease limited to the convexities of the face, often have periocular lesions, usually do not flush as rosacea patients do, and may have unilateral disease. It is thus difficult to consider this condition to be nosologically or pathophysiologically within the rosacea spectrum.

While we recognize the difficulty of proposing new names for disease states deeply ingrained in the literature, we suggest *granulomatous facial dermatitis* as a diagnostic category for this condition. Other variants of granulomatous facial dermatitis have been described and have not always been placed under the umbrella of rosacea. Examples include the more recently described facial Afro-Caribbean childhood eruption (FACE),[49] granulomatous perioral dermatitis,[50] and the older lupus miliaris disseminatus faciei.[51]

Implications of rosacea subtypes

Most investigations to date do not specify the defining characteristics of their patient population and have not subcategorized patients. In 1989 Marks opined that one reason for a lack of progress in understanding the pathogenesis of rosacea was that rosacea may represent more than one disease entity.[52] Some studies do state that erythematotelangiectatic or papulopustular subtypes were studied and often the findings are quite variable. In a study by Lonne-Rahm et al,[2] it was discovered that 7 of 7 ETR patients experienced stinging when 5% lactic acid solution was applied to the cheek. However, only 68% of the PPR patients and 17% of control subjects reacted with the perception of stinging. When the role of the adnexal structures, vascular reactivity, and other potential etiologic factors in rosacea are being investigated, it is essential that the patient population be clearly defined as to the basic definition of rosacea and the particular subtype studied.

The use of these subtypes also allows better education of patients. Not all are at risk for the development of the large bulbous nose; not everyone needs to make lifestyle changes or avoid irritants. Also, there is clearly the expectation that varying therapeutic interventions will be necessary, that responses will not be uniform, and that adverse reactions may be prominent in one subtype but nearly absent in another.

PATHOPHYSIOLOGY

The cause of rosacea remains unknown. Several factors have been implicated in its pathogenesis, some based on the evidence of scientific investigation, others on anecdotal observation. Proposed etiologic mechanisms can be grouped into the following categories: vasculature, climatic exposures, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities, and microbial organisms. However, a central paradox remains; how does one explain the varied clinical expressions of rosacea through one isolated mechanistic theory? It is likely that rosacea's distinct nosologic subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) represent heterogeneous responses to a combination of these purported

factors. In addition, all of these implicated triggers are experienced by healthy persons who never go on to develop the symptoms or signs of rosacea. Consequently, rosacea-prone persons must have an inherent sensitivity to these ubiquitous triggers.

Vasculature

Perhaps the most-cited pathogenic theories about rosacea center on inherent abnormalities in cutaneous vascular homeostasis. Most of these theories are based on the prominent facial flushing seen in many rosacea patients.[4,5,53] Flushing, or transient, erythema is controlled by 2 vasodilatory mechanisms: humoral substances and neural stimuli.[54] Wilkin demonstrated that proportional increases in cutaneous blood flow were the same in both the forearm and the face after neurally mediated (oral thermal challenge) and direct smooth muscle–mediated (nicotinic acid test) signals.[9] That flushing in ETR and PPR is visibly concentrated on the face can be explained by the fact that baseline blood flow is increased in the face[55-57] and that facial vessels are larger, more numerous, and nearer to the surface than in other areas of the body.[58] Consequently, both neural mechanisms and circulating humoral agents produce flushing reactions that may be visibly limited to the face.[9,11]

Dysregulation of thermal mechanisms has been proposed by some to cause the vasodilation in rosacea.[13,59-61] The normal physiologic response to hyperthermia is an increased flow of blood from the face to the brain, presumably to aid in intracranial cooling. In one small study, this response to hyperthermia was absent in 4 rosacea patients (measured in the angular veins near the orbit) as compared with 2 control subjects.[13] Studies have also shown that when challenged with thermal stimuli, rosacea patients flush more easily and in a more pronounced fashion than control subjects.[13,59-61] In a study of 24 patients with ETR, Wilkin demonstrated that it was the temperature rather than the caffeine of coffee that generated flushing responses.[11] Theoretically, increased oral temperature leads to a heat exchange mechanism in the carotid arteries that signals the hypothalamus to trigger vasodilation.[11] Albeit interesting, this theory has not yet facilitated the treatment of facial flushing in rosacea patients, except for the suggested use of ice chips in the mouth during such thermal stimuli as warm showers or hot weather.

Interest in the role of substance P—the mediator now thought to induce flushing in carcinoid[62]—has waned owing to a lack of substantial evidence in previous studies.[63-65] Other proposed mediators have included vasoactive intestinal peptide,[66] gastrin,[6,67,68] serotonin, histamine, and prostaglandins.[69,70] Robust experimental support for any of these soluble mediators is lacking.

Climatic exposures

Many authors have endorsed the notion that rosacea results from the caustic effects of climatic exposures that damage both cutaneous blood vessels and dermal connective tissue.[3,5,17,71-77] Several authors have observed that rosacea is often found in persons occupationally exposed to heat.[6,73]

The pivotal role of sunlight is supported by the distribution of erythema and telangiectases on the facial convexities. Sun-protected areas, such as the supraorbital and submental areas, are typically spared. The association with fair skin and light eyes,[73] the predilection for disease flares in early spring,[73] and the tendency to spare the young are all consistent with a pathogenic role for solar radiation. In addition, actinic elastosis is prominent in skin biopsy specimens from rosacea patients.[74]

In contrast, epidemiologic studies demonstrate that only 17% to 31% of rosacea patients report worsening of symptoms by sunlight.[78,79] Several photoprovocation studies in rosacea patients have failed to show heightened skin sensitivity to the acute effects of ultraviolet radiation.[73,79-82] Despite the increased prevalence in those with fair complexion, rosacea does occur in black patients.[83,84] However, these findings should be considered cautiously. Even patients with proved photoinduced disorders, such as tumid lupus, are often unaware of the sun's effect on their skin, especially when the effect is slow to appear.[85] In addition, subacute and chronic changes that are most relevant to rosacea are much more difficult to identify without ample population sizes and adequate control subjects matched for age, skin type, and history of sun exposure.

Dermal matrix degeneration

Much interest has surrounded the dermal connective tissue and its role in the pathogenesis of rosacea. Histopathologic studies have demonstrated both endothelial damage and matrix degeneration in skin specimens of affected patients.[73,74,86-89] It is clear from other research fields that cutaneous vascular damage can precede matrix degeneration. In a study of ultraviolet light effects on rats, dilated and tortuous vessels were detected well before matrix abnormalities became apparent.[90] In persons with diabetes, microangiopathy can lead to alterations in perivascular connective tissue.[91] The common premise is that abnormal vascular homeostasis leads to leaky vessels and delayed clearance of serum proteins,

inflammatory mediators, and metabolic waste, all of which may lead to matrix degeneration.

Alternatively, some authors support a primary role for damaged connective tissue in inducing vascular pathology.[58,74,86,88] Solar radiation may alter lymphatic and blood vessel function via damage to the dermal support network of elastic and collagen fibers.[58,72] This matrix-centered theory holds that telangiectasia, persistent erythema, profound flushing, and edema are all caused by poor connective tissue support for cutaneous vessels, resulting in the pooling of serum, inflammatory mediators, and metabolic waste.[52] Despite prominent ectasia, vessels in rosacea maintain the ability to dilate and to constrict in response to local (ethylnicotinate privine and dimethyl sulfoxide)[6] and systemic (adrenaline, noradrenaline, histamine, and acetylcholine)[60,61] vasoactive agents. These findings provide some support for the central role of matrix degeneration, since vessel reactivity remains intact.

Soybe described the benefit of massage therapy in cases with prominent edema, and he theorized that lymphatic abnormalities might play a role in pathogenesis.[73] Delayed clearance of inflammatory cells, soluble mediators, and cellular degradation products result in prolonged inflammation and tissue damage. As in the lower extremities, lymphedema in the central part of the face could result in connective tissue hypertrophy and fibroplasia. This mechanism has been theorized to produce some of the findings in rhinophyma.

Chemicals and ingested agents

Dietary factors and gastrointestinal diseases have historically been theorized to influence rosacea. Although spicy foods, alcohol, and hot beverages are known to trigger flushing reactions in rosacea patients,[11,79] the prevailing evidence at present does not support a primary role for diet or other gastrointestinal factors in the pathogenesis of rosacea. Through misrepresented media imagery, the "plethoric facies" and "drinker's noses" of phymatous rosacea are often presumed to result from excessive alcohol consumption. However, medical support for this theory is lacking. Epidemiologic studies that have focused on the relationship between rosacea and alcohol have been confounded by barriers to medical access, by poor patient compliance, by inaccuracies in alcohol-consumption history provided by alcoholic persons, and by inadequate control populations.[12,73,92] Alcoholism can manifest itself in the skin in a variety of ways, many of which are likely the result of cirrhosis rather than the direct effect of alcohol.[12]

Certain medications can induce flares in rosacea or produce rosacea-like dermatoses. Amiodarone has been reported to induce rosacea and multiple chalazia.[93] Topical steroids have most often been considered triggers or causal agents in rosacea-like eruptions.[43,94-97] Occasionally, rosacea patients have been reported to have dramatic flares even after using nasal steroids for allergic rhinitis.[98] Nicotinic acid is also known to stimulate flushing reactions in rosacea patients.[9] Acneiform eruptions that resemble rosacea have also been reported in association with supplements that contain high doses of vitamins B_6 and B_{12}.[99,100]

Pilosebaceous unit abnormalities

Controversy exists as to whether the papules and pustules of rosacea are follicularly based. In a study of 108 biopsy specimens, including 74 from patients with PPR and 24 from patients with ETR, Marks and Harcourt-Webster found abnormalities of the hair follicle in only 20% of the 74 papules or papulopustules subjected to biopsy.[74] In addition, perifollicular inflammatory infiltrates were found in only 51% of these specimens. Ramelet and Perroulaz conducted a similar study of French patients with rosacea.[86] All 75 specimens contained perivascular infiltrates, while only 13 (17%) were judged to be predominantly periadnexal in nature. In a histologic study of 12 patients with ETR, Motley, Barton, and Marks described common lymphohistiocytic infiltrates that were predominantly in a perivascular, not perifollicular, location.[88]

It is, however, documented that the glandular type of rhinophyma is a follicularly based inflammatory process.[19] Therapies such as topical and oral antibiotics, which may be targeting follicularly based organisms such as *Propionibacterium acnes,* are effective in rosacea. These medications include benzoyl peroxide, which is well tolerated and effective in PPR and GR patients but has no inherent anti-inflammatory action. In addition, the role of *Demodex,* a follicularly based organism, has been the subject of repeated investigation as a possible causative factor in rosacea.

Additional studies are warranted to investigate the role of a follicular-based inflammatory process in rosacea. Future studies should subdivide patients into the appropriate rosacea subtypes. In the histopathologic studies of Marks and Harcourt-Webster[74] and Ramelet and Perroulaz,[86] only a minority of patients underwent investigation with serial sectioning. It is our experience that horizontal sections are best able to reveal follicular-based disease in non-scalp skin. When further studies are undertaken in

the various subtypes of rosacea, it would be of interest to document whether the lesions subjected to biopsy are early or late in evolution, what the frequency and density of *P acnes* is, especially in therapeutic protocols with antibiotics, and how the sebaceous gland size and secretion rates are characterized. While Burton et al[101] and Pye, Meyrick, and Burton[102] found normal secretion rates and lipid composition in affected rosacea skin sites, we believe that subdividing the patients into subtypes may reveal variable results.

Microbial organisms

Demodex. *Demodex* is a common inhabitant of normal human skin, and its role in human disease is a matter of controversy. Several authors have proposed that *Demodex* plays a pathogenic role in rosacea.[3,17,75,76,103-112] Historical support derives from observations that *Demodex* prefers skin regions most often affected by rosacea, such as the nose and cheeks.[41,113] The tendency for clinical manifestations of rosacea to appear later in life parallels the increase in *Demodex* mite density that occurs with age.[114-117] In addition, studies have demonstrated immune responses in rosacea patients that may be directed against *Demodex* antigens.[80,118,119] Grosshans et al reported that in 22% of 31 rosacea patients, *Demodex*-specific antibodies were found in the serum.[118] Another study showed a predominance of helper-inducer T cells in infiltrates that surrounded *Demodex* mites.[119]

Numerous studies have been performed to report prevalence rates for *Demodex* infestation in rosacea patients.[3,16,17,75,76,105,106,120] However, the sampling methods employed have been extremely variable (eg, adhesive bands, skin scrapings, skin impressions, comedo extraction, hair epilation, cyanoacrylate skin surface biopsies, and punch biopsies), making little value of any interstudy comparison. *Demodex* is also known to vary with patient age and the skin site sampled. In addition, *Demodex* is found in a large number of healthy persons. In fact, with more modern and sensitive techniques, the prevalence in healthy adults approaches 100%.[76,116,117,121,122] Consequently, the simple identification of *Demodex* is by no means proof of pathogenesis. It is the density of mites[76,106,113] or their extrafollicular location[103,111,123-125] that is of greater importance in the assessment of pathogenesis.

Techniques that employ cyanoacrylate surface biopsies are extremely sensitive.[76,106,110] Studies by Forton and Seys and by Erbagci and Ozgoztasi both independently demonstrated that the density of *Demodex* was significantly higher in patients with papulopustular rosacea than in age-matched control subjects.[106,126] In contrast, both studies failed to demonstrate statistically significant increased mite densities in patients with ETR. This lack of statistical power could represent a true lack of difference in mean mite counts, or could be the result of a much smaller sample size of patients with ETR than that of patients with PPR investigated in both studies. Another limitation is that skin surface biopsies can show *D folliculorum* residing only superficially in the follicle. Thus this technique misses mites deeper in the follicle and *D brevis* mites that reside in the sebaceous glands.

After having observed mites or fragments in extrafollicular inflammatory infiltrates, some investigators believe that *Demodex* mites are responsible for some of the skin lesions in rosacea.[107,127-129] Forton demonstrated a statistically significant relationship between the presence of *Demodex* and perifollicular, lymphohistiocytic inflammation in 69 biopsy specimens from rosacea patients.[129] Other studies have not supported these findings.[74,86,124] In both Ramelet and Perroulaz's and Marks and Harcourt-Webster's large histopathologic studies of rosacea, there was no correlation between perifollicular inflammation and the presence of *Demodex*.[74,86] However, these results can be questioned by the fact that *Demodex* is not easily detected on histologic preparations. Only 19% of 108 specimens were found to contain *Demodex* mites in the study by Marks and Harcourt-Webster, and only 3% of 75 specimens in that of Ramelet and Perroulaz. With a more exhaustive approach, one would expect higher densities of *Demodex*.

Lastly, it has been hypothesized that the beneficial effects of metronidazole on rosacea may be related to an antiparasitic effect toward *Demodex*. Mites, however, can survive high concentrations of the drug.[130] Others claim that oral and topical metronidazole formulations are effective via an immunologic pathway or by a metabolite with activity against *Demodex*.[6,131,132] However, studies have shown that clinical resolution of rosacea after treatment with tetracycline[76] or topical 3% sulfur ointment[133] did not affect the *Demodex* population. Whether *Demodex* is truly pathogenic or simply an inhabitant of follicles in rosacea-prone skin remains the subject for future study.

Helicobacter pylori. Some controversy has also persisted concerning the possible role of *H pylori* in rosacea.[134-139] Interest emerged from statistically unsupported, yet historically ingrained, associations between rosacea and gastrointestinal diseases, such as hypochlorhydria, gastritis, and

abnormal jejunal mucosa.[53] Others have observed that the seasonal fluctuations of rosacea mimic those of peptic ulcer disease, a condition that is now known in most cases to be caused by *H pylori* infection. In addition, metronidazole, a common treatment for rosacea, is an effective agent against *H pylori*.

H pylori is the most common infection in human beings.[140] Hampering the study of this organism's role in rosacea is its ubiquitous presence and its benign nature in most people.[141] Robust support for a causal association between *H pylori* and rosacea does not exist. Several studies have demonstrated high prevalence rates of *H pylori* in rosacea patients,[142-145] some even in comparison with age- and sex-matched controls.[146] Other studies, however, did not corroborate these data.[134, 147-151] In addition, several studies have demonstrated either clinical improvement in rosacea[134] or a lack thereof[151,152] at the conclusion of therapeutic regimens aimed at the eradication of *H pylori*. None of these studies, however, was fully controlled for all the confounding variables known to influence *H pylori* prevalence, such as sex, age, socioeconomic status, and medications, or was statistically powered to account for the ubiquitous nature of *H pylori* infection in the general population.

With all these data generated from prior studies, we can conclude with some certainty that the following statements are reasonable:

- *H pylori* is commonly found in patients with rosacea and in the general population; and
- treatments aimed at eradicating *H pylori* may also influence the clinical outcome of rosacea.

Despite inconclusive studies, interesting hypotheses concerning the possible pathogenic role of *H pylori* have recently been generated. It is known that *H pylori* infection increases several vasoactive substances such as histamines, prostaglandins and leukotrienes, and various cytokines. However, these vascular mediators are found only with *H pylori* strains that produce a specific cytotoxin, CagA (cytotoxin-associated gene A) or VacA (vacuolating-associated gene A). Szlachcic et al compared 60 rosacea patients with age- and gender-matched nonulcer dyspepsia control subjects.[146] They found that when infected with *H pylori*, 67% of rosacea patients, versus only 32% of controls, had positive findings for CagA. In addition, these patients had elevated systemic levels of tumor necrosis factor α and interleukin 8. After eradication of *H pylori* infection, symptoms of rosacea disappeared in almost all patients (51 of 53) and tumor necrosis factor α and interleukin 8 levels normalized.[146] Despite these interesting findings, robust support for the role of *H pylori* in the pathogenesis of rosacea is lacking.

FUTURE STUDIES

Many aspects of rosacea require further investigation. It is our hope that this manuscript will stimulate some of these efforts. One area to approach in regard to pathophysiology is the possible follicular nature of the papules and pustules. Researchers should also investigate the role of *P acnes* in the formation of these inflammatory lesions. Concerning investigation into *Demodex* and *H pylori*, we suggest that future efforts be directed elsewhere. Despite exhaustive efforts in numerous studies, clear evidence for a pathogenic role in rosacea has not been demonstrated for either of these organisms.

The role of hormones in producing the flush responses, the oiliness of facial skin in glandular rosacea, and the utility of spironolactone in papulopustular rosacea or glandular rosacea are yet to be defined. In addition, further investigations of the potential extrafacial symptoms of rosacea, the inherent sun sensitivity of rosacea skin, and possible circulating vasoactive mediators are warranted. The contribution of a genetic predisposition to sun damage, responses to other climatic conditions, and flushing responses should be studied. It is clear that certain populations are more susceptible and that many patients with rosacea have similarly affected relatives. What genetic factors are important and why?

Potentially bridging the divergent hypotheses of ultraviolet light exposure and vascular dysregulation on rosacea pathogenesis, Kosmadaki et al demonstrated an increased expression of vascular endothelial growth factor messenger RNA levels after in vitro irradiation of cultured keratinocytes, an effect that appeared to be independent of tumor necrosis factor α.[153] Certainly, this remains an area ripe for future investigation, as the complex interplay between matrix degeneration and vascular homeostasis in rosacea has yet to be clearly defined.

As we theorize that the pathogenesis of rosacea varies with the phenotypic subtype, we emphasize the importance of clearly defined criteria and subtype inclusion in future studies. Additionally, control populations should be properly matched in terms of factors known to influence rosacea phenotype, such as age, sex, and cumulative sun exposure. Certainly many more questions than these remain. It is hoped that curiosity has been stimulated, the need for continued research highlighted, and progress in

understanding this common and important condition will follow.

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