PART 2
ROSACEA

"He has a quiet way of walking, as if he is afraid of alarming the truth and frightening it away"

-Ippei Okamoto on Albert Einstein

1. INTRODUCTION: BACKGROUND ON ROSACEA

Epidemiology

Rosacea is a common condition in both males and females, although more common in the latter group. While the disease affects children as well as the elderly, rosacea is usually found in middle-aged adults. Fair-skinned patients of European descent appear to be more commonly affected, although it is believed that in darker skinned individuals, the pigmentation may serve to mask the erythematous component of rosacea. Although thought to be a “curse of Celts,” rosacea has been also observed to be common among all Indo Eurasians. [1]

Rosacea is a common problem, with data from Sweden revealing a prevalence as high as 10%, [2] and 2012 data from as the National Rosacea Society estimating that rosacea may affect over 16 million Americans.[3] While rhinophyma (rosacea affecting the nose) is more commonly seen in men, with the more severe cases seen after the age of 40 years, [4,5] ocular rosacea (rosacea affecting the eyes) appears to affect both sexes equally. [6]

Characteristics and Classification

Rosacea is characterized by (a) redness, photosensitivity and telangiectasia; (b) overgrowth of sebaceous glands (sebaceous hyperplasia); and (c) presence of pustules and acne, with or without residual scarring. Any combination of the above, and sometimes all three, may be seen in any one patient. Usually the face is involved, with frequent involvement of the nose, forehead, paranasal cheeks, upper lip and chin. At the very least, the cheeks are red (hence the term rosacea), with enlarged oil glands (sebaceous hyperplasia) and prominent pores (follicular orifices). The patient is usually photosensitive with multiple superficial capillaries (telangiectasia) associated with photosensitivity. Unusual severity may be observed in certain patients. These include granulomatous rosacea, sometimes called rosacea fulminans, ocular rosacea, acne rosacea with pustules and acneform lesions, cystic rosacea (rosacea conglobata) among others. Rhinophyma is seen when the sebaceous hyperplasia involving the nose becomes extreme.

The National Rosacea Society [7-9] has established a classification system that identifies four distinct subtypes based on clinical presentation: (a) erythematotelangiectatic, (b) papulopustular, (c) phymatous, and (d) ocular.

Current Knowledge of the Pathogenesis of Rosacea

At present, the underlying cause of rosacea has yet to be fully worked out, and treatment to date has remained largely symptomatic. However, new information has led to several theories which may serve to improve the understanding of the pathophysiology of rosacea, leading to identification of precipitating factors and improved management of the disease.

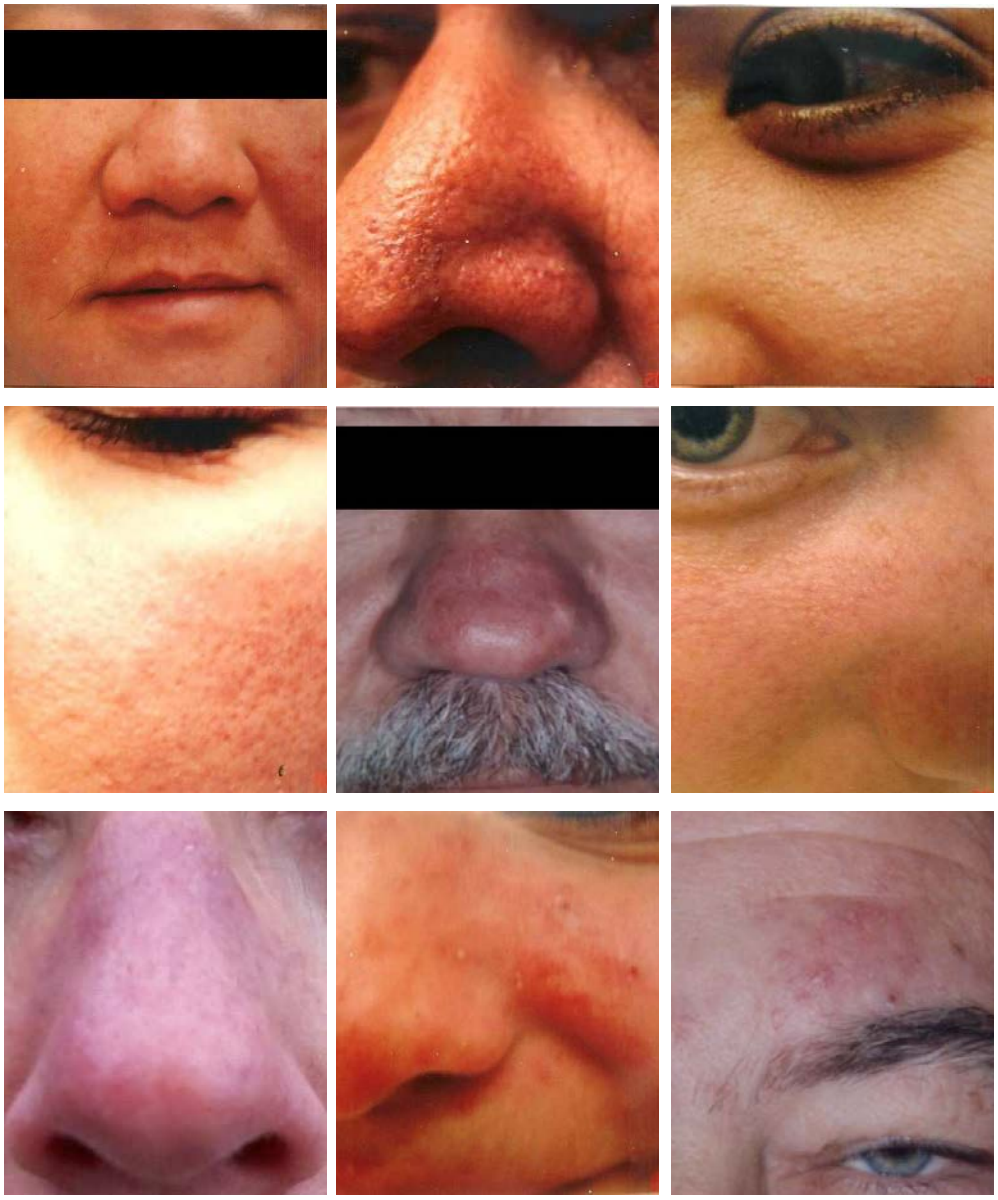

Figure 1: Various manifestations of Rosacea symptoms

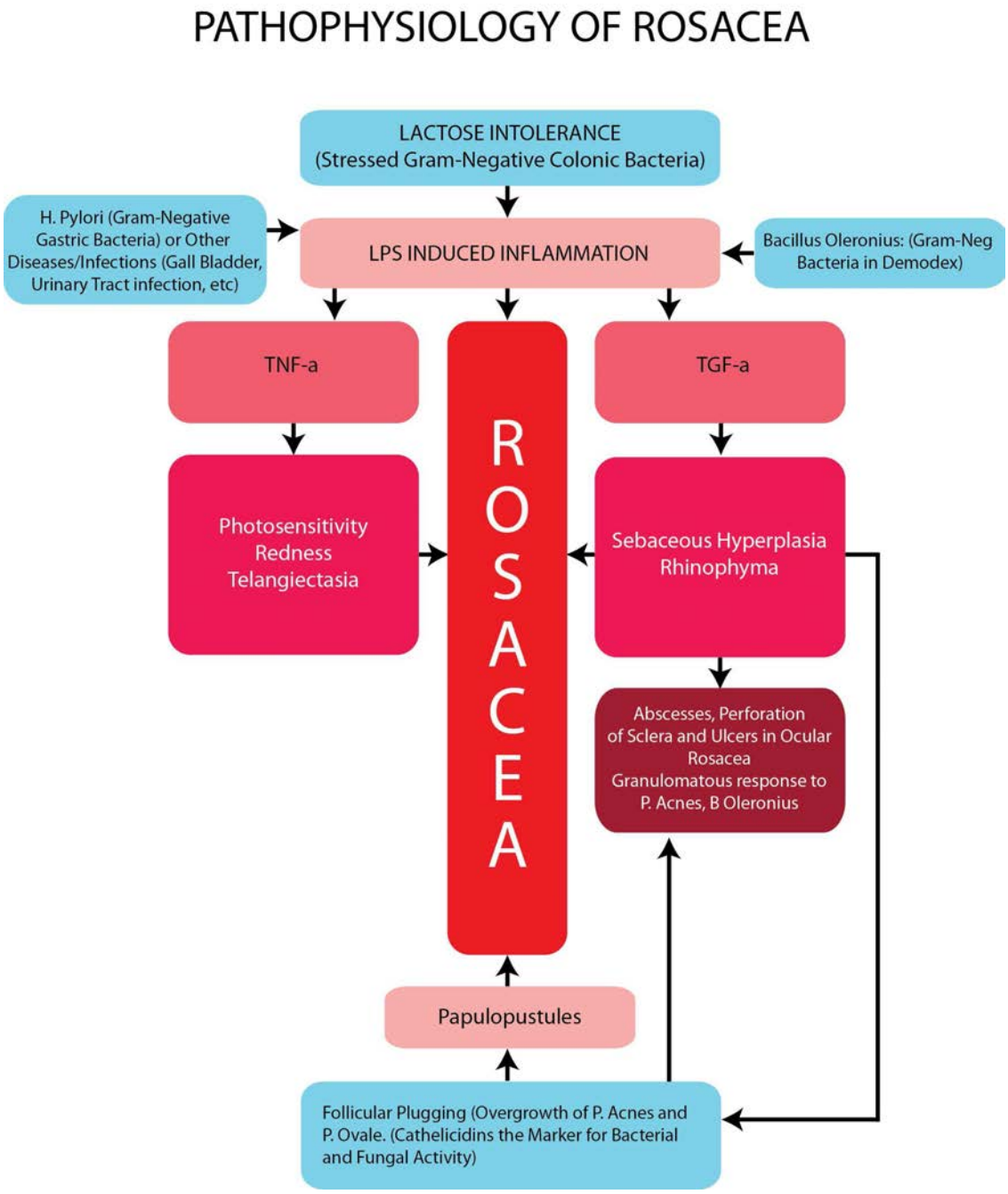

Figure 2: Pathophysiology of Rosacea

"*Science originates from curiosity and bad eyesight*"

-Bernard de Fontenell

2. FACTORS AGGRAVATING ROSACEA: GENERAL INFORMATION

Because of the multiple dilated capillaries (telangiectasia) associated with photosensitivity, rosacea is worsened by histamine releasers and vasodilators. These include heat and sunlight, aspirins, alcohol, foods containing iodine (sea-foods and shellfish), chocolates and nuts, tyramine in cheeses, and preservatives such as nitrites and sulfites, among others. Rosacea is also worsened by topical photosensitizers such as colognes, deodorant soaps, furocoumarins in limes, and pine pollen, as well as by oral photosensitizers such as hydrochlorothiazide and sulfa drugs, among others. Although these products are not considered to be related to the basic cause of rosacea, nevertheless, for symptomatic reasons, it is still useful to avoid both histamine releasers and photosensitizers

Several studies confirm the inflammatory component of the disease. These studies [10-13] show the presence of elevated levels of inflammatory cytokines. Interleukin-1α (IL-1α) and interleukin-1β (IL-1β), as well as

gelatinase B (metalloproteinase-9) and collagenase-2 (metalloproteinase-8) have been found in tear fluid in patients with ocular rosacea. [11] Surprisingly, although TNFα elevations were observed in tear fluid in ocular rosacea, the elevations were not significant. [10] This observation is surprising because the increased expression [11] of ICAM-1 and HLA-DR (known inducible markers of TNFα activity [14] by conjunctival epithelial cells in patients with rosacea should indicate the presence of TNFα-mediated inflammation. The lack of local evidence of TNFα secretion in rosacea is interesting because this finding apparently suggests that the TNFα may be generated elsewhere, lending some truth to the suggestion that rosacea may indeed be a "skin manifestation of systemic disease".

The beneficial effects of doxycycline and minocycline in rosacea may point to the role of LPS (lipopolysaccharide)- induced inflammation in rosacea due to the fact that minocycline has been shown to attenuate LPS-induced inflammation [15] by reducing LPS-induced Toll-like receptor-2 (TLR-2). [15] This may be particularly significant since TLR-2 expression has been reported to be increased in rosacea. [13] These findings strongly suggest that LPS from the cell membranes of Gram-negative bacteria may play a key role in inducing inflammation in rosacea.

We have observed the frequent association of rosacea with lactose intolerance. Most humans are lactose intolerant since they lose the ability to produce lactase in their intestines by the age of 5 years. The undigested lactose spills into the colon and increases the osmotic pressure of the colon, thereby making it difficult for the colonic bacteria to survive. The Gram-negative colonic bacterial cell membranes contain LPS, which are released by dead and dying bacteria in the colon of lactose intolerant individuals. In our animal model for lactose intolerance, we fed rats with a sugar (dextran sulfate), which in the rats were undigested in the colon, thereby raising the osmotic pressure in the colon. [16] The colonic bacteria expressed heat shock protein 60 (hsp 60), a stress protein, prior to fragmentation of their cell membranes. [16] The presence of membrane fragmentation signifies release of LPS from the dead colonic bacteria. [16] The released LPS, also known as endotoxin, serve as antigenic epitopes for triggering LPS-induced inflammation. [16,17]

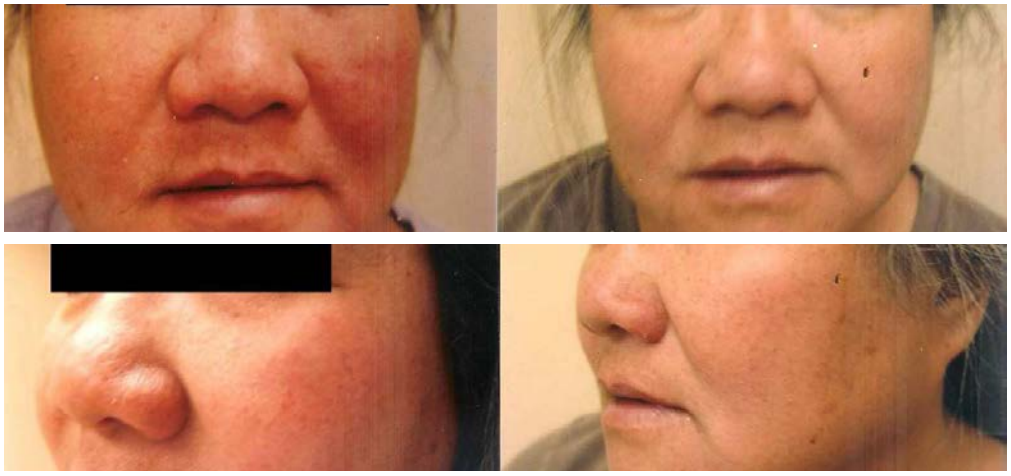

Figure 3: Patient showing erythema and sebaceous hyperplasia (left panels), both of which improved after 6 months (right panels) with a lactose-free diet, curcumin gel and oral minocycline.

Unlike contact allergens which stimulate skin CD8+ T lymphocytes that do not produce large quantities TNFα, LPS-induced inflammation in the colon result in generation of abundant TNFα through the IL-17/1L-23 pathway. [18-20] The LPS binds to the CD14/TLR-4/MD2 receptor complex, which promotes the secretion of proinflammatory cytokines in immune cells. The expression of hsp 60 stress protein [16] by the dying bacteria also serve as epitopes to activate dendritic cells, [16] which are also capable of generating large amounts of TNFα. Lipopolysaccharides have been shown to induce Th17-polarized response by dendritic cells through IkBα kinase/NFkB and p38 MAPK pathways. [17,18] Lipopolysaccharides have also been shown to be capable of inducing TNFα-primed dendritic cells to produce IL-23 and induce resting CD4 cells to secrete IL-17, resulting in secretion of high levels of TNFα by inflammatory cells. [18,19] Both IL-23 and IL-17 have been found to be important in colonic inflammation, while blockade of these cytokines by their relevant monoclonal antibodies have resulted in reversal of the colonic inflammation. [20,21] The amount of TNFα secreted parallels the erythema and photosensitivity symptoms in rosacea.

Growth factors produced by colonic inflammatory cells in lactose intolerant individuals may induce patients to develop features of acanthosis-nigricans-like syndrome. This manifests itself by heavy eyelids, with multiple folds (Figure 5) and dark circles around the eyes (Figure 6). These have been shown to improve with a lactose-free diet (Figures 5 and 6). Eyelid changes are frequently seen in young children prior to the development of frank rosacea (Figure 7). In older individuals, the spectrum of heavy eyelids, rosacea and sebaceous hyperplasia are frequently seen together in the same patient (Figure 8). Because these changes resolve with a lactose free diet, it is believed that the same pathophysiology induced by lactose intolerance may occur in both children and adults (Figures 5-8). The clinical differences may be due to the duration of lactose exposure, and the dose of lactose ingested.

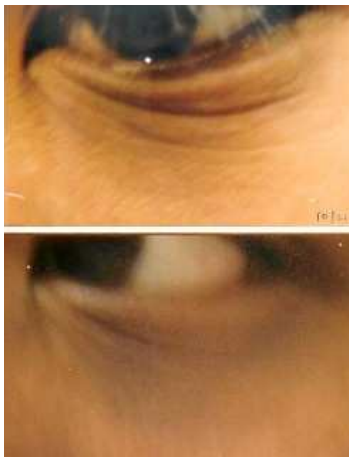

Figure 4: Teenager with prominent eyelids associated with lactose intolerance (upper panel). Note improvement after 6 months on a lactose-free diet and curcumin gel (lower panel).

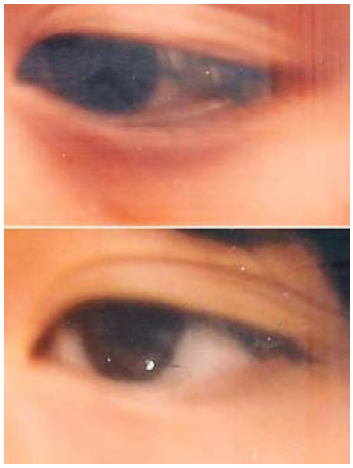

Figure 5 shows a 9 year old patient with dark circles around the eyes and mild rosacea with early enlargement of sebaceous glands (upper panel). Note improvement after 6 months on a lactose-free diet (lower panel).

It is of interest that LPS-induced target inflammation may also include mast cells, [22] which have been shown to produce TNFα when stimulated by LPS. [22} The production of TNFα and IL-6 by mast cells in LPS-induced inflammation is particularly relevant in rosacea, since erythema from mast cell release may contribute to the redness in rosacea patients. Furthermore, the role of TNFα in producing photosensitivity [23] would also explain the distribution of rosacea over the sun-exposed areas of the cheeks, eyelids and nose.

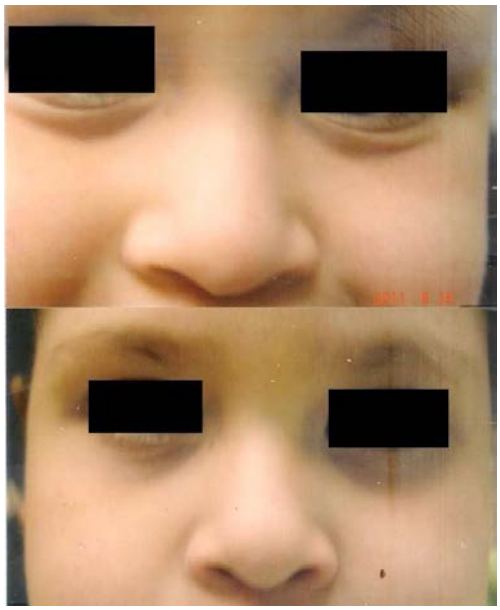

Figure 6: Two-year old child with heavy eyelids associated with lactose intolerance. Note early rosacea and early enlarged sebaceous glands (upper panel), with improvement after 3 months of lactose curtailment (lower panel). The patient was taking calcium and vitamin D supplements.

Figure 7: Rosacea patient with heavy eyelids, sebaceous hyperplasia and photosensitivity (upper panel). Improvement after 6 months with a lactose-free diet and topical curcumin gel under sunscreen (lower panel).

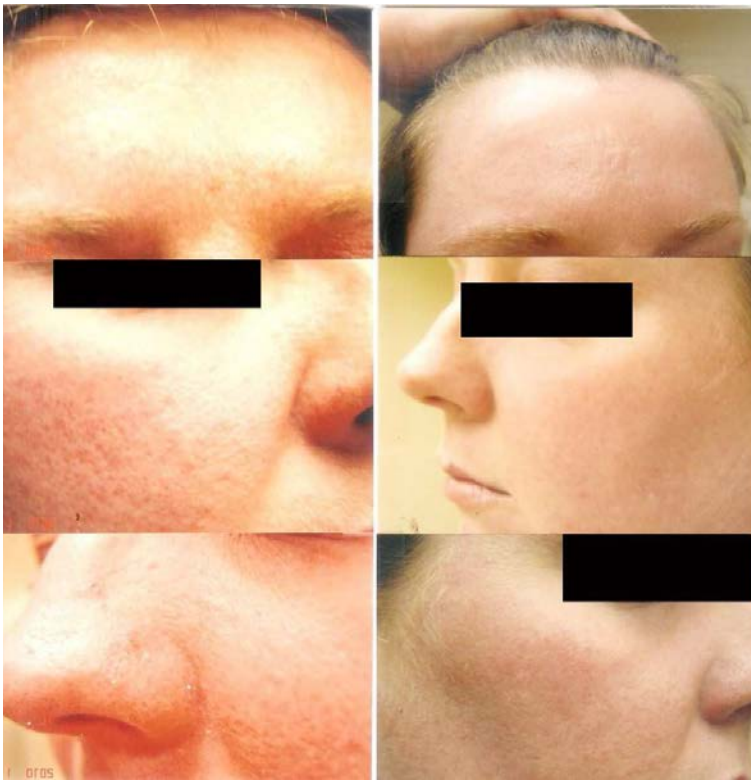

Figure 8: The erythematous rosacea associated with sebaceous hyperplasia is also benefited by curcumin gel applied underneath a layer of sunscreen. The patient was also put on a lactose-free diet, which was responsible for the improvement in sebaceous hyperplasia as well as decreased photosensitivity observed in the follow up photos nine months later (see right panels). Using curcumin gel under the sunscreen not only benefits the photosensitivity but also prevents the pores from being clogged by the cream base of the sunscreens.

Finally, one must also consider underlying disease associated with elevated of TNFα as possible causes of rosacea. These include infections, such as sinus and ear infections, periodontal and dental infections, gall bladder disease, kidney stones, and urinary tract infections. These infections are frequently due to gram-negative bacteria (LPS-induced inflammation). In addition, autoimmune diseases, such as lupus erythematosus, may present with rosacea and photosensitivity.

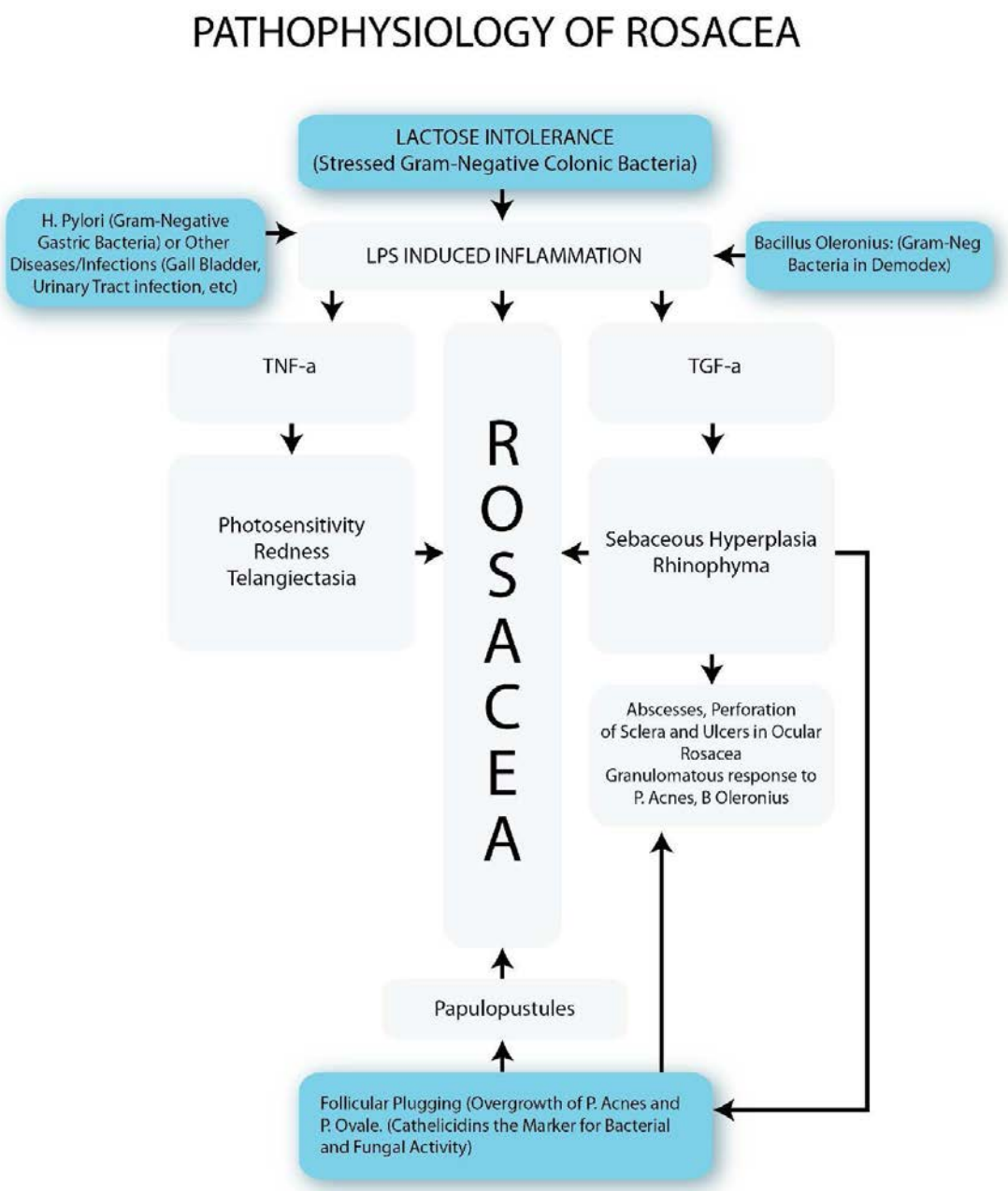

Figure 9: Causative Factors that Aggravate Rosacea

"*If you are too open-minded, your brains will fall out*"

-Lawrence Ferlinghetti

3 CAUSATIVE FACTORS THAT UNDERLIE ROSACEA: PATHOPHYSIOLOGICAL CONSIDERATIONS

In considering the “etiology” or “causative factor” on rosacea, we have defined the following criteria: (a) the features of rosacea should be reversible, at least in the early stages, by the removal of this proposed causative factor; (b) recurrence of rosacea should be able to be avoided by continued removal of the causative factor; and (c) the features associated with rosacea can be explained pathophysiologically by incrimination of the causative factor. Based on the above criteria, the following causative factors have been proposed to be related to the pathophysiology of rosacea:

1. Helicobacter pylori: Causative Role in Rosacea in Selected Individuals

In certain rosacea patients, the presence of gram-negative bacteria may serve as sources of LPS-induced inflammation which aggravating their rosacea. An example is Helicobacter pylori (H. pylori), which colonizes gastric

mucosa in patients with increased acid secretion. This gram-negative bacterium, found in the gastric mucosa of patients with gastritis and peptic ulceration, has been linked to rosacea since the 1990s. [24-26] In fact, rosacea has been considered by some to be a cutaneous marker of H. pylori infection. [26] Following eradication by combination therapy which included omeprazole (20 mg bid), clarithromycin 500 mg bid, and metronidazole 500 mg bid, the symptoms of rosacea resolved in 51 of 53 rosacea patients with positive H. pylori verified by 13C-UTB test. Plasma TNFα and IL-8 were reduced after the combination therapy by 72% and 65% respectively. [27] These findings support a role for H. pylori in a specific group of rosacea patients with positive tests for H. pylori in their gastric mucosa.

2. Demodex folliculorum: Role of Bacillus oleronius in rosacea in patients with Demodex folliculorum

The increase in numbers of the Demodex folliculorum (D. folliculorum) mite population in rosacea was reported as early as 1993, [28] with higher densities of D. folliculorum in the areas of facial skin affected by rosacea compared to subjects with normal skin. [28] However, it has only been recently appreciated that the causative agent may be a bacterium called Bacillus oleronius (B. oleronius) associated with the human skin parasite, D. folliculorum. Bacillus oleronius is a Gram-negative bacterium possessing antigens capable of stimulating inflammatory cells in 73% of patients with rosacea compared with only 29% of control subjects. [29] Two relevant peptides were isolated – a 62 kDa immunoreactive stress protein, and an 83 kDa protein related to an enzyme regulating the stress response of the bacterium. [29] There was a positive correlation between serum immunoreactivity to D. folliculorum-associated Bacillus proteins and erthematotelangiectatic rosacea. [30] The relation of the antigenic proteins from Bacillus oleronius to heat shock proteins (hsp) is significant in view of the demonstration by our laboratory of the presence of hsp 60 in LPS-dependent inflammation in our animal model for lactose intolerance. [16] The hsp 60 is an epitope (antigen) capable of activating γδT-cells and induce the secretion of large amounts of TNFα. [17-19] These findings support the role of B. oleronius and its parasitic vector, D. folliculorum, in the pathogenesis of rosacea. In particular, the identification of stress protein elements suggests

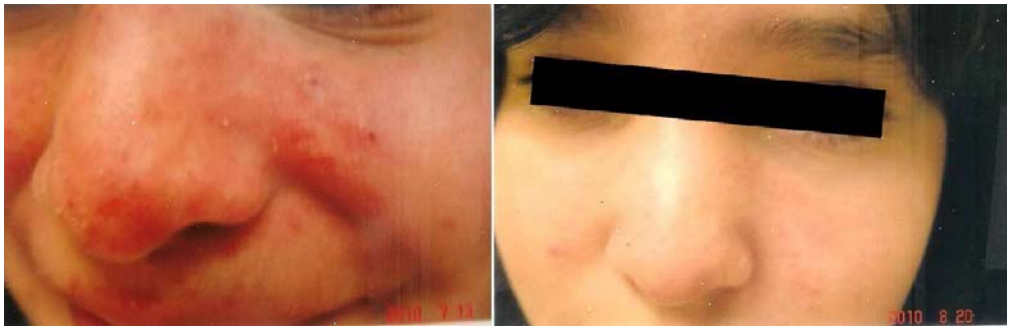

Figure 10: Superinfection of the skin by pathogenic gram positive bacteria such as Staphylococcus aureus and Streptococcal sp should be considered in patients with a history of worsening rosacea with pustules. The pustules and skin should be swabbed for bacterial culture and sensitivity, and the antibiotic selected based accordingly on the results of the culture. This is a patient with erythematous rosacea aggravated by Staphylococcus aureus superinfection. Improvement is observed with oral keflex, lactose-free diet and curcumin gel.

the possibility that disease may be caused by stress proteins produced either by the Demodex mite or its microbiota when their survival is threatened, such as by over-population or over-treatment. [29,30] It is also likely that the sebaceous hyperplasia induced by underlying lactose intolerance (see below) may support the overgrowth of Demodex in the pilosebaceous follicles in patients with rosacea. The inflammatory response caused by B. oleronius may be responsible for the pustular component of rosacea. [29] Rosacea patients may benefit from reduction in the size of sebaceous glands achieved with a strict lactose-free diet.

Antibiotic therapy may be indicated in patients that do not respond to other therapy. Since B. oleronius is sensitive to tetracycline, [29] the tetracycline family of antibiotics, including doxycycline and minocycline, may be helpful in treating B. oleronium-induced rosacea.

3. Lactose Intolerance

Lactose intolerance may also be a major causative factor of rosacea, and one that fits the above discussed criteria. We have observed that rosacea frequently develops months or years after the patient has ingested a diet containing lactose. Most children lose the ability to secrete lactase, the enzyme which helps digest lactose milk sugars, by the age of 5 yrs. East Asians are very lactose intolerant, and for this reason, East Asians generally

do not use dairy products in their diet. The frequent inclusion of dairy products in Europeans and Indo-Eurasians may account for increased prevalence of rosacea in these populations. [16]

Pathophysiology of Rosacea in Lactose Intolerant Individuals:

In lactose-intolerant individuals, the undigested lactose spills into the colon, and raises the osmotic pressure of the colon. The rise in osmotic pressure interferes with the survival of the colonic bacteria, with resultant release of exposed bacterial cell membranes containing lipopolysaccharides (LPS). Lipopolysaccharides are superantigens, capable of stimulating γδ T cells to produce large amounts of TNFα. The photosensitivity in rosacea is due to TNFα, who is responsible for the redness and photosensitivity of sunburns. In addition, growth factors, such as transforming growth factor-α (TGFα), are also produced by the activated T cells and macrophages, and TGFα is responsible for the growth of oil glands (sebaceous hyperplasia and rhinophyma) as well as cysts, skin tags, warty growths over the face and back resembling seborrheic keratoses. [31] In addition, the development of acanthosis nigricans with thickened dark circles around the eyes, and thickened hyperpigmented skin over the neck and axilla, may also be observed in lactose-intolerant individuals. The chronic inflammation in the colon associated with lactose intolerance in patients consuming dairy products may be associated with constipation, diarrhea, hemorrhoids, diverticulitis, colon polyps and colon malignancy. [31]

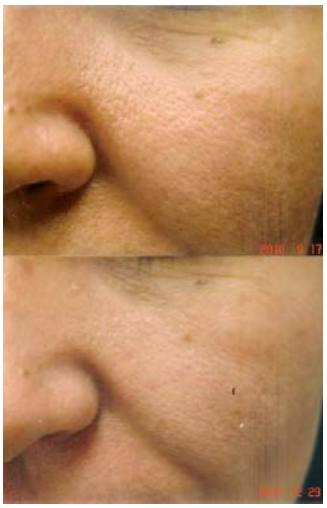

Figure 11: Shows a rosacea patient with mild erythema but prominent sebaceous hyperplasia which improved after 3 months (bottom panel) with a lactose-free diet and curcumin gel.

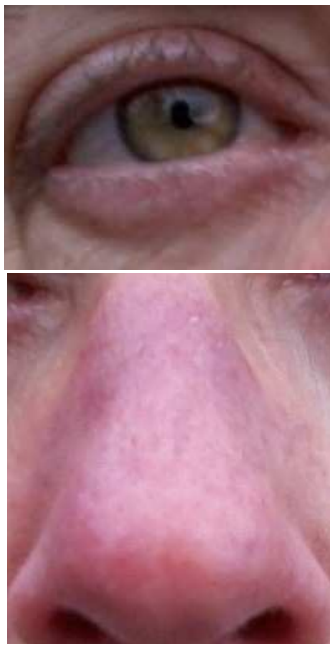

Figure 12 upper and lower panels Shows a patient with rosacea aggravated by chronic nasal allergies. The condition is aggravated also by constant use of topical steroid sprays.

Rosacea can also be aggravated by TNFα secreted by internal infections. In allergic rhinitis, Figure 12, and chronic sinusitis (Figure 13, next page), the rosacea is often associated with prominent erythema of the nose and paranasal cheeks. Sebaceous hyperplasia may be present because of associated lactose intolerance, but is not a prominent finding in such patients, who provide a long history of nasal and sinus problems. The condition is also aggravated by topical steroid sprays used by the patients. The rosacea in such patients is difficult to reverse because of their underlying allergies and chronic use of these steroid sprays aggravated also by constant use of topical steroid sprays.

In one animal model of lactose intolerance, [16] rats were fed a sugar the rats were incapable of digesting. This sugar, dextran sulfate, spills undigested into the colon, thus resembling the undigested lactose in lactose-intolerant humans. In another group of rats fed less dextran sulfate (half-dose), the rats did not die, but were observed in follow-up studies to develop colonic malignancy (Leung FW. Personal communication). Sacrificed animals showed expression of the stress protein, hsp 60, by day three. [16] Heat shock protein 60 (Hsp60) was demonstrated to be produced by stressed colonic bacteria subjected to the environment of increased osmotic pressure in the colon due to the presence of the undigested sugar (dextran sulfate). Hsp 60 is the epitope capable of activating γδ T cells. The γδ T cells are known to be capable of generating high levels of cytokines and growth factors, including TNFα and TGFα. [16] The TNFα is responsible for erythema and photosensensitivity in rosacea, and TGFα for the sebaceous hyperplasia and features of acanthosis nigricans. [31]

4. Other Cutaneous and Extra-Cutaneous Infections Aggravating Rosacea

Rosacea is frequently associated with underlying internal disease, including overgrowth of H. pylori associated peptic problems, sinusitis, gall-bladder disease and even urinary tract infection. The cytokine, TNFα, released by these bacterial associated problems, induce

photosensitivity, resulting in redness and telangiectasia over the sun-exposed distribution of the face. Superinfection of rosacea lesions by gram positive bacteria with superantigenic properties (Staphylococcus aureus/MRSA and/or Streptococcal sp.) may also worsen rosacea. These bacteria contain superantigens that activate 20% of the T lymphocytes, thereby producing large quantities of TNFα. In cases with worsening erythema and pustules, cultures of the skin and pus from the pustules should be performed and sent for bacterial culture and sensitivity, with oral antibiotics instituted according to the culture results.

5. Role of follicular plugging and P. acnes in rosacea with acneform lesions

The pathophysiology of rosacea with acneform lesions is similar to that in acne vulgaris, with the added component of rosacea and sebaceous hyperplasia. The sebaceous hyperplasia promotes the growth of lipophilic organisms that feed on the sebum produced by the sebaceous glands. These include Proprionibacterium acnes, and Pityosporum ovale (a lipophilic yeast) and occasionally other bacteria including the non-pathogenic Staphylococcus epidermidis. The acneform pustules and abscesses may heal with scarring. It is therefore important to prevent plugging of the hair follicles in order to prevent secondary acneform lesions and abscesses that may lead to scarring (See page 37, Acne Chp 9 "Treatment Protocol: Controlling Cystic Acne & Treatment of Residual Scarring".

Follicular plugging may also aggravate ocular rosacea, with the antigenic components of Bacillus oleronius and relevant microorganisms promoting significant secretion of TNFα, which may lead to corneal ulceration, scarring and scleral perforation. Sebaceous hyperplasia, often associated with underlying lactose intolerance, may thus promote the growth of microorganisms, with their increased antigenic overload.

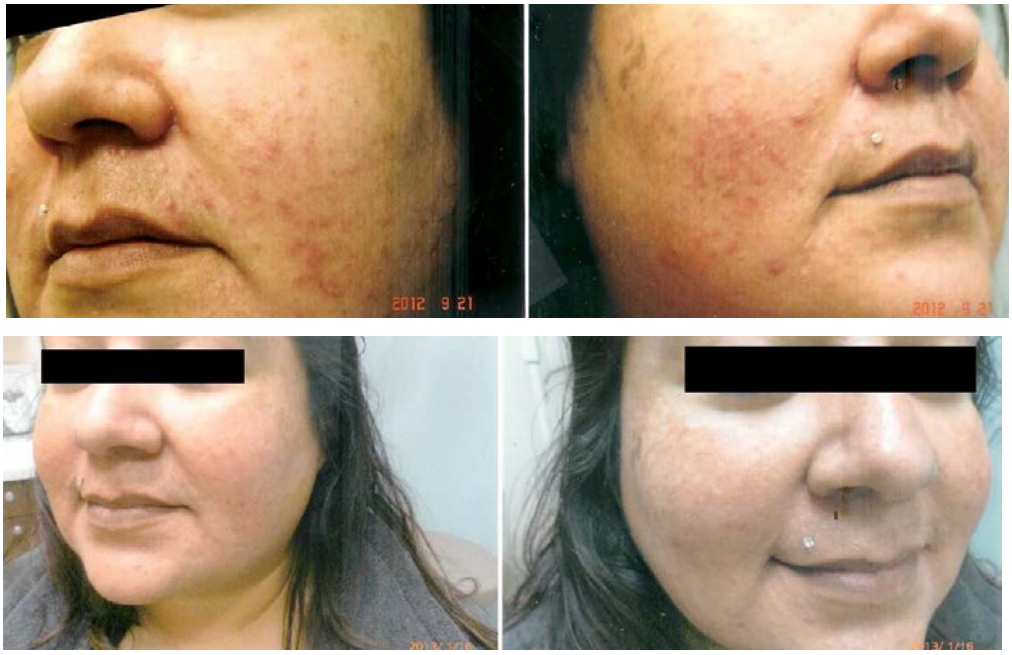

Figure 13: Rosacea with pustules aggravated by lactose intolerance (major) and by sinus infections (minor). Improvement was achieved with adequatae treatment of her sinus infection, lactose-free diet, oral doxycycline and curcumin gel.

The Demodex mites that feed on skin scales and sebaceous secretion may be overpopulated in lesions of sebaceous hyperplasia. The skin mite, Demodex folliculorum, which mainly colonizes hair follicles, may also aggravate ocular rosacea both by their physical presence and through associated microorganisms (B. oleronius, present in the gut of the Demodex mite). However, because many patients with Demodex do not have rosacea, it is possible that the disease may have developed from prior follicular plugging caused, for example, by the use of extraneous products, such as moisturizers, creams and sunscreens.

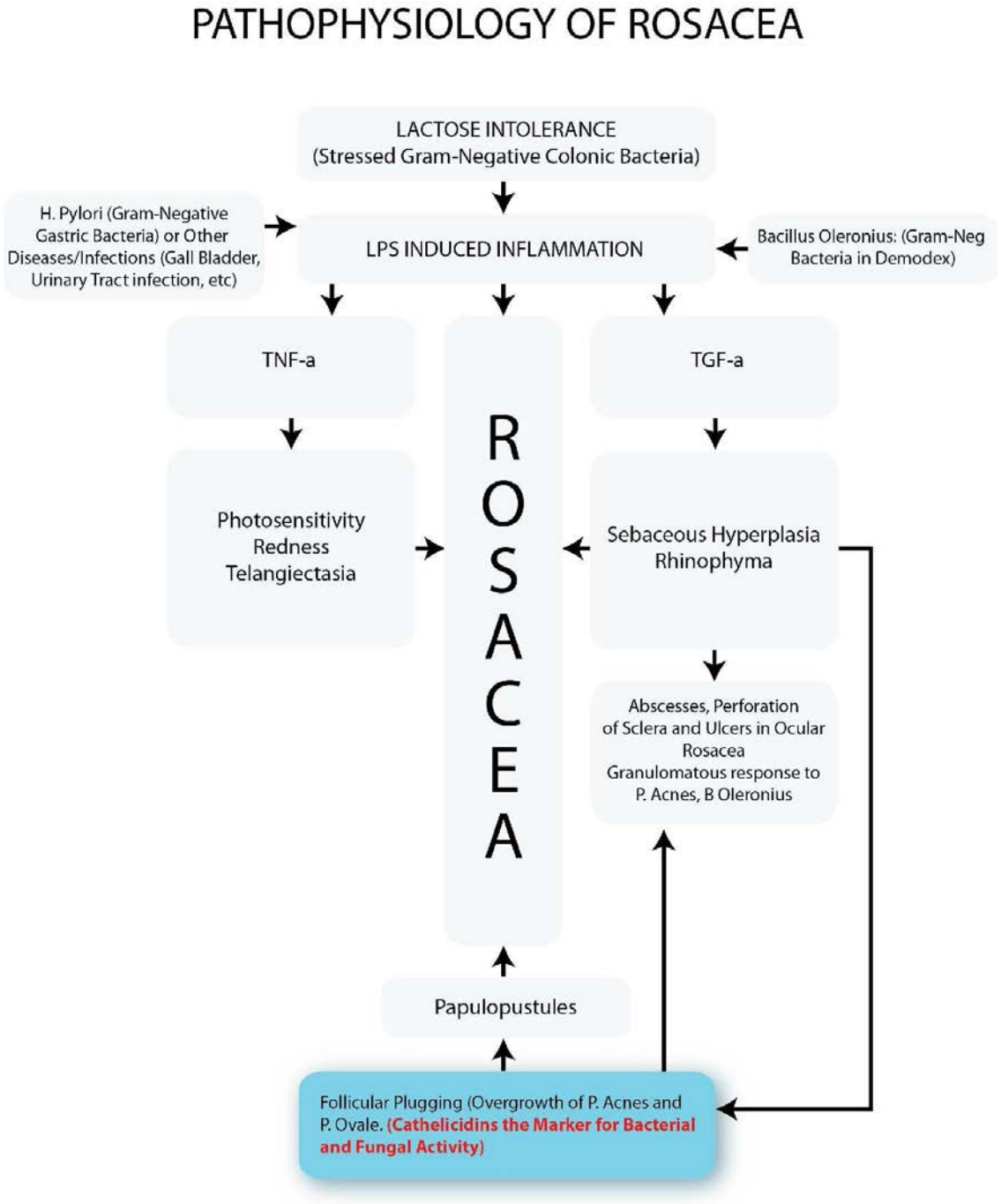

Figure 14: Cathelicidins, one of the causative factors in aggravation of Rosacea

"*Why is it that doctors call what they do 'practice'?*"

-Bertrand Russell

4 CONTROVERSIAL ROLE OF CATHELICIDINS IN ROSACEA

More recently, attention has been focused on a group of antimicrobial peptides (small proteins) known as cathelicidins, which has been observed to be increased in a number of inflammatory skin conditions, including psoriasis, rosacea and hidradenitis suppurativa. [32] Increased abundance and activity of cathelicidin and kallikrein 5 (KLK-5) has been implicated in the pathogenesis of rosacea. [33] Moreover, it has been shown that doxycycline can prevent cathelicidin activation by inhibiting the generation of the cathelicidin peptide LL-37 from its precursor protein hCAP-18, a process dependent on KLK activity. [33]

Cathelicidins belongs to a family of small host defense peptides produced by neutrophils and epithelial cells. [34] The secretion of this peptide is increased under conditions of inflammation and is believed to have immunomodulatory and antimicrobial function. LL-37 has been demonstrated to inhibit neutrophil apoptosis. [34] It is possible that this activity may promote the formation of neutrophil-containing pustules in inflammatory lesions of rosacea.

The cathelicidins are expressed as large precursor molecules with a highly conserved pro-domain known as the cathelin-like domain (CLD). Cathelin-like domains have high degrees of sequence homology to cathelin, a protein belonging to the cystatin family of cysteine protease inhibitors. Recently, the crystal structure of human cathelin-like domain (hCLD) of the sole human cathelicidin (LL-37) was described. [35] The investigators found that both the pro-cathelicidin (hCAP-18) and the LL-37 inhibited the growth of Gram-negative bacteria, while the hCLD itself lacked antimicrobial function and did not inhibit the cysteine protease, cathepsin L. [35] The authors believe that the cysteine scaffold represents an ancestral structural platform from which proteins evolved divergently, with some losing inhibitory functions. Their elevations in rosacea may be secondary to the increased bacterial microbiota in rosacea.

Since cathelicidins function in host defence, doubt must be cast upon the current strategy of treating rosacea with long-term doxycycline, which has been found to interfere with the generation of the LL-37 peptide (shown to possess anti-bacterial activity) from its precursor protein, hCAP-37. However, doxycycline may be indicated in the treatment of pustular rosacea through its activity on cathelicidin-mediated anti-apoptotic effects on neutrophils. [33,34]

"Who says nothing is impossible? Some people do it every day"

-Alfred E. Neuman

5 TREATMENT OF ROSACEA

These are my suggested steps to improve the symptoms of Rosacea:

1. Reduce sun-induced damage and repair photodamaged skin:

a. Curcumin Gel: Topically applied curcumin gel has been observed to have anti-inflammatory, anti-photodamage [37,38] as well as anti-scarring [39] properties. Curcumin is the active ingredient in the spice turmeric, and has been shown to alleviate the symptoms of sunburns, photosensitvity, and rosacea.

b. Sunscreen: Jucidicous use of sunscreen may be helpful in UV light-induced erythema in rosacea sufferers. It is advised that those with rosacea should avoid chemical blocker sunscreen (or sunsceen with any or all of the following ingredients: Octylcrylene, Avobenzone, Octinoxate, Octisalate, Oxybenzone, Homosalate, Helioplex, 4-MBC, Mexoryl SX and XL, Tinosorb S and M, Uvinul T 150, Uvinul A Plus), as they may irritate the skin

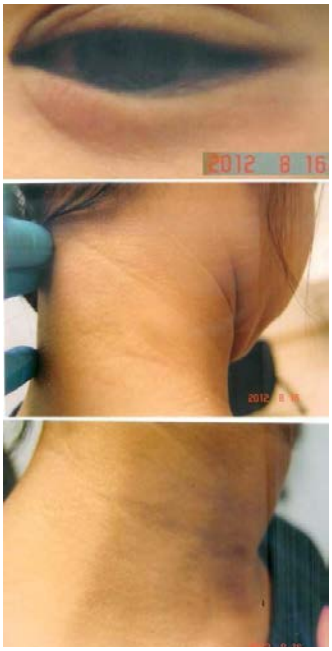

Figure 15: Ten year old patient with heavy eyelids (upper panel) and early acanthosis nigricans affecting the skin of the neck, which was both thickened (middle panel) and hyperpigmented (bottom panel).

Frequently the acanthotic changes affecting the eyelids are associated with features of early acanthosis nigricans affecting the neck may be observed in both children (Figure 15) and adults (Figure 16).

and worsen symptoms. Physical blocker sunscreen without nanoparticles containing zinc oxide or titanium dioxide may be better tolerated. (I do not recommend products containing nanoparticles because of the potential damage to cell membranes.)

2. Lactose-Free Diet:

The most common aggravator of rosacea is cytokine-induced photosensitivity caused by the release of TNFa (tumor necrosis factor-alpha), a protein secreted by colonic inflammatory cells associated with lactose intolerance. Both rosacea and enlarged sebaceous glands (sebaceous hyperplasia) have been observed to improve within an average of 3-6 months with strict curtailment of lactose in the diet.

3. Avoidance of histamine releasers, topical photosensitizers and oral photosensitizers:

The common histamine releasers include heat and sunlight, hot soups and drinks, hot spicy foods, aspirins, alcohol, foods containing iodine (sea-foods and shellfish, sea-weed and sushi, iodized salt), chocolates and nuts, tyramine in cheeses, preservatives such as nitrites and sulfites (preserved fruits and meats), monosodium glutamate (MSG), certain artificial sweeteners (aspartame), yellow orange dye (tartrazine) in canned fruits and drinks, strawberries, and high doses of vitamin C.

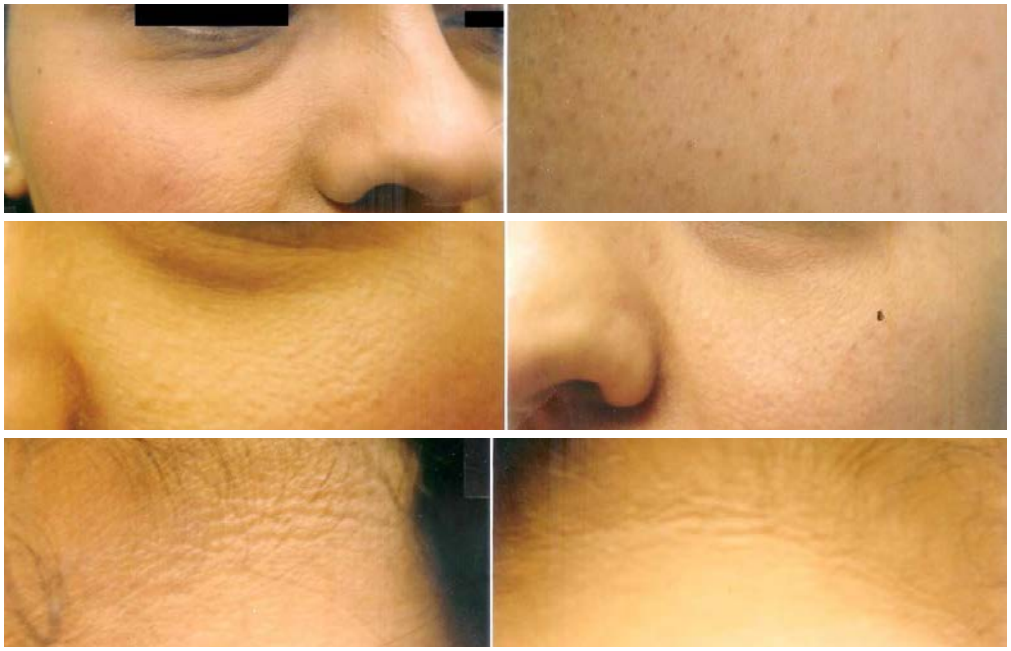

Figure 16: Patient with lactose intolerance with rosacea, sebaceous hyperplasia, heavy eyelids (upper left, and acanthosis nigricans affecting the neck (bottom left) associated with early skin tags of the neck (upper right). Improvement in the neck after 6 months on a lactose-free diet, was associated with improvement in the eyelids and sebaceous hyperplasia. (middle and bottom right) The patient also applied curcumin gel to the affected areas.

The common topical photosensitizers include colognes, deodorant soaps, furocoumarins in limes and lemons, and pine pollen, among others. Limonene, a scent ingredient and solvent naturally ocurring in the rind of citrus fruit, are also frequently found in cosmetic products and shampoos.

Oral photosensitizers, such as hydrochlorothiazide diuretics used for treating hypertension, and sulfa drugs, frequently contaminating poultry, may worsen rosacea, in particular erythematous/telangiectactic rosacea. Many other drugs, including phenothiazines, and even doxycycline may also cause photosensitivity.

4. Prevention and treatment of pustular rosacea:

Use of doxycycline or minocyclines to control pustules in pustular rosacea, with cessation of the drug when pustules are resolved. Doxycycline may be used to inhibit proliferation of sebaceous glands, to control the

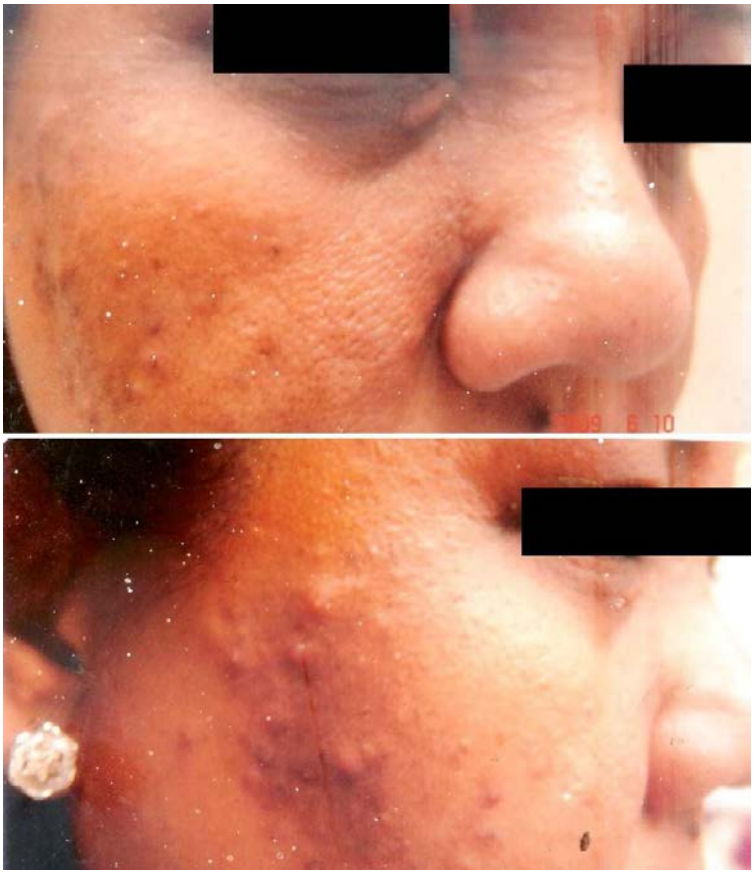

Figure 17: Patient with lactose intolerance with dark circles around her eyes, sebaceous hyperplasia, cysts around her eyes, and deep scarring acneform abscesses over her preauricular cheeks from the use of moisturizers and conditioners in the shampoo.

population of P. acnes in blocked follicles, and to block cathelicidin-mediated effects. It is also thought that members of the tetracycline family may also be effective against B. oleronius. [29]

5. Control of Pityosporum ovale, a lipophilic yeast:

Overgrowth of Pityosporum ovale is suspected if the rosacea is associated with erythema with superficial scaling suggestive of seborrheic dermatitis. [36] The patient may benefit with a course of oral Diflucan (fluconazole).

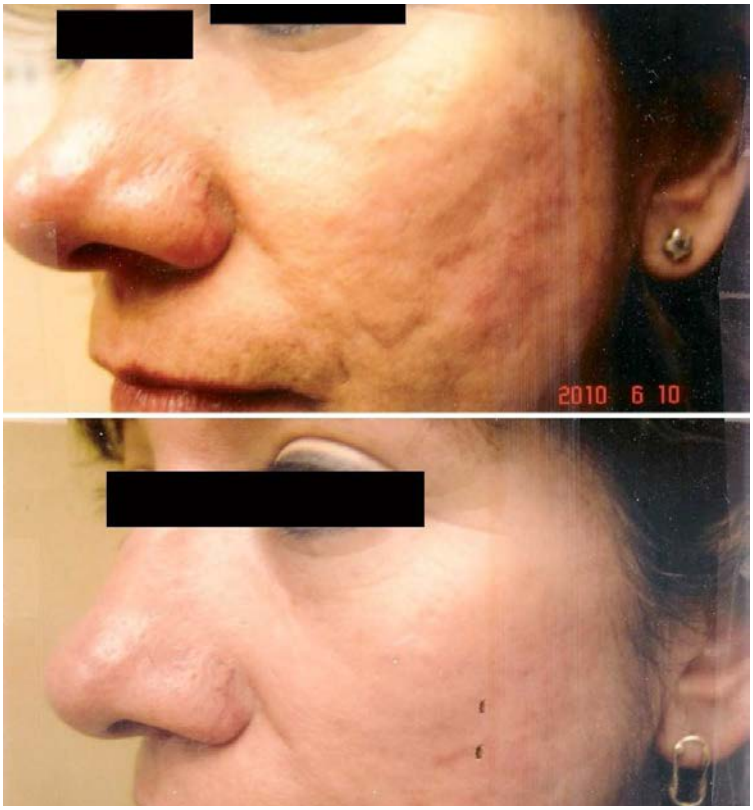

Figure 18: Improvement of melasma is seen after 6 months with a lactose-free diet, assisted by the curcumin gel (applied all over) and localized application of sunscreen over the curcumin gel in the hyperpigmented areas. Note improvement of both the sebaceous hyperplasia and melasma.

6. Prevention and treatment of acneform lesions:

Avoiding acneform eruptions is achieved by avoiding follicular plugging of the hair follicles. Acneform lesions in rosacea are treated in a similar manner as for acne vulgaris. This includes measures to unplug plugged follicles with topical retinoic acid 0.025% at bedtime, topical curcumin gel during the day, with considerations of high dose oral vitamin A in rosacea with severe acne.

Oral doxycycline 100 mg twice daily or minocycline 100 mg daily is added for the pustular component of acne. The patient avoids hair mousse, conditioners in the shampoo, oily products and moisturizers. In my practice, I

also advise the use of curcumin gel under make-up and sunscreens to prevent clogging of pores. Topical clindamycin solution 1% may be used judiciously for spot treatment of pustules. It is recommended that the patient uses glycerin soap for washing, with tailoring of washing to the amount of oils capable of draining to the skin surface. When the skin feels dry, washing with soap is avoided and water alone is used to wash until the skin feels moist again.

7. Removal of precipitating factors:

a. Treatment of H. pylori, if present.
b. Treatment of urinary tract infection, if present.
c. Removal of gall bladder in patients with underlying cholecystitis, if clinically indicated.
d. Treatment of hay-fever and nasal allergies if present
e. Treatment of sinus infections, if present.

8. Adopting a healthy lifestyle:

Lifestyle changes to improve general health and healing to damaged skin may also be helpful. These include eating a diet abundant in fruits and vegetables, with strict avoidance of dairy products, and cutting back on meats and fatty foods. Other measures to improve general health such as an approved diet and exercise program with appropriate weight control are also helpful. Finally, efforts to maintain a regular daily routine, and healthy sleep habits will decrease stress, which often leads to aggravation of rosacea symptoms.

Rosacea, like acne, is a treatable disease which often involves an accumulation of symptoms. Identifying the causes can not only alleviate present symptoms, but prevent future exacerbation of symptoms as well.

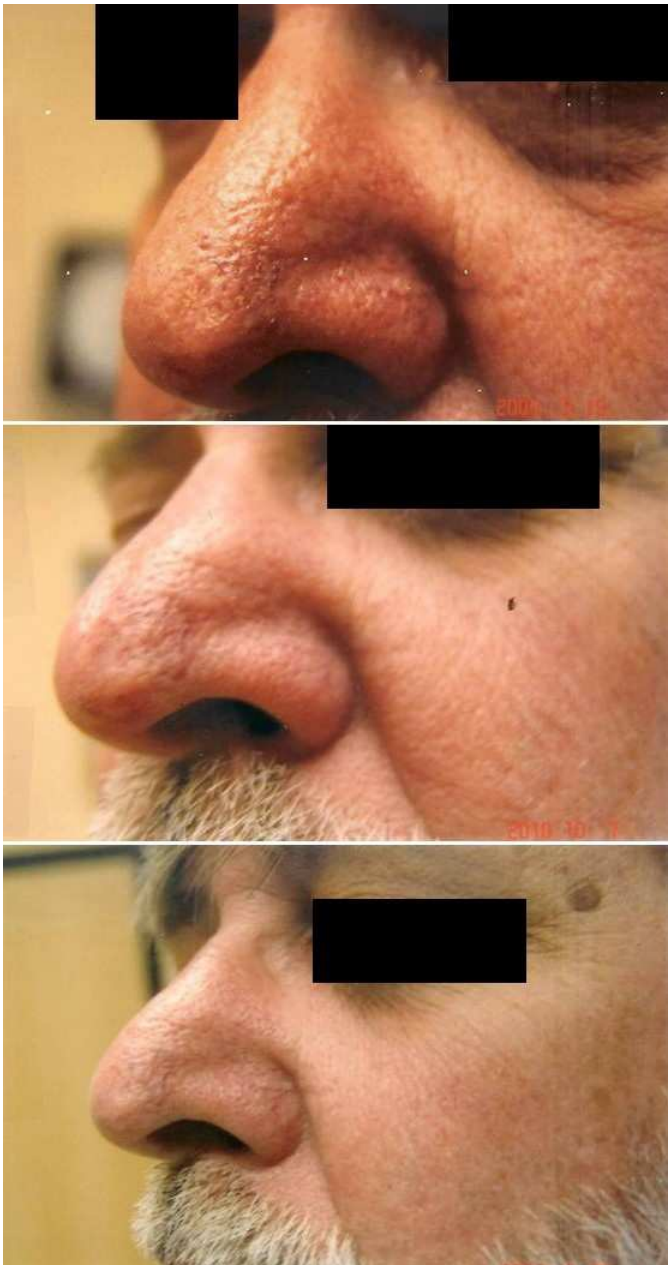

Figure 19: Erythematous rosacea with sebaceous hyperplasia may be associated with increased TNFα associated with lactose intolerance, and patients will benefit from strict curtailment of lactose in the diet.Patient with erythematous rosacea with sebaceous hyperplasia (top panel), improved after 6 months (middle panel) and 12 months (bottom panel) on a lactose-free diet, and curcumin gel.

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