BELOW THE SURFACE

A Guide to Better Understanding Acne & Rosacea

by Madalene Heng, MD, FRACP, FACD, FAAD

This book is dedicated to my family

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CONTENTS

All the interests of my reason, speculative as well as practical, combine in the three following questions:

1. What can I know?
2. What ought I to do?
3. What may I hope?

-Immanuel Kant

INTRODUCTION

The idea to write this small book came about because of comments from patients, such as: “I have had acne since the age of 12 years, and I am now 70. I should have outgrown acne by now!” and “I have tried so many types of treatments for rosacea and it does not go away". This book is not meant to be an all inclusive textbook, but rather a summary of my knowledge and extensive clinical experience treating these conditions. Much of it is information from published studies, while the rest are common sense knowledge and clinical observations of what works in my practice. It is meant for the discerning patient who wants more in-depth information than is usually available, and may be useful for non-specialist healthcare providers. The book also provides updated information from my long clinical and research experience with curcumin therapy for skin diseases. (Curcumin is derived from the natural spice turmeric, and has potent anti-inflammatory actions useful in the treatment of many skin disorders.)

Acne and acneform pustules and abscesses can be considered among the most common of skin conditions. The severity of acne in different

individuals may vary from occasional pimples during puberty, to severe disease associated with scarring and psychological debilitation. Acne has many causes and forms, but by and large, the problem in most patients with acne vulgaris is due to plugging of the hair follicles (comedones). In this book, I have concentrated on the most common cause of acne - acne vulgaris. Granted that there is probably a genetic component, which is largely related to the amount of oil secreted by the sebaceous glands, or the tendency to develop comedones, there is also a large environmental component, which is largely responsible for the clinical problem, i.e. clogging of the follicular pores- the basic cause of acne. The pores need to be unplugged before the acne can improve. The understanding of what promotes follicular plugging or clogging of pores is basic to both treatment, and prevention of acne. Failure to appreciate the importance of follicular plugging, and the factors that promote follicular plugging will lead to a life-time of out-breaks of acne, with failed treatments and attendant risks of scarring. On the other hand, a deeper understanding of what aggravates follicular plugging will go a long way towards clinical improvement and clearance, withdrawal from therapy and prevention of future outbreaks of acne.

The same can be said about rosacea, with its characteristic erythema and enlarged sebaceous glands. Many patients are treated for years without substantial benefit do so because the underlying cause is largely ignored. Understanding of the basic causative factors that underlie rosacea can result in clinical improvement of the condition.

Finally, I would like to explain why I have included rosacea in a book with acne. Acneform lesions and pustules are frequently found in patients with rosacea. Acne patients, with accompanying rosacea and sebaceous hyperplasia tend to have worsening disease as they grow older, and sebaceous hyperplasia becomes the main cause of acne in older individuals. Since both diseases are related and frequently present in the same patient, I have chosen to talk about both acne and rosacea in the same book.

Madalene Heng MD, FRACP, FACD, FAAD
Professor of Medicine/Dermatology
UCLA School of Medicine

PART ONE
ACNE

"*That is the essence of science: Ask an impertinent question, and you are on the way to a pertinent answer*"

-Jacob Bronoski

1. NEW THEORIES ABOUT ACNE AND ACNEFORM DISORDERS

Acne and acneform disorders are among the most common clinical problems in modern society, affecting a wide range of age groups from pre-teenagers through to middle age. However, the causes of these conditions is often misunderstood by many who treat them, and the complications which result in residual scarring can be devastating to the acne sufferers. The scars are frequently treated with laser therapy, which may further damage the skin, distorting the function of the hair follicles, and result in further scarring and persistent acne symptoms.

Depending on certain clinical features, acne may be known as comedonal acne, cystic acne (acne conglobata), acne varioliformis, acne cosmetica, acne medicamentosa, lithium-induced acne, oil folliculitis, among others. The names must not detract from the common denominator in the production of acneform lesions, which is the presence of clogged pores that prevent drainage of sebum to the skin surface.

The role of a bacteria, Proprionibacterium acnes (P. acnes) as a causative factor in acne also needs to be defined since blaming this organism as the fundamental cause of acne may lead to inappropriate treatment of the disease. In addition, inflammation and immune responses have been implicated in the pathophysiology of acne, and, in my opinion, too much focus on their importance has clouded the understanding of their roles in the pathogenesis of acne. Finally, proper understanding of the contribution of topical preparations, toiletries and cosmetics will go a long way to prevent acne and avoid aggravation of this common skin problem.

Early investigators of acneform lesions suggest that acne may be a disease caused by inflammation of the pilosebaceous apparatus (the structure comprised of the hair follicle and sebaceous glands) with P. acnes causing pustules and abscesses.[1,2] However, the findings that non-inflamed lesions in acne (first visible at the start of menstruation in acne-prone individuals for example) do not contain P. acnes, that acne comedones appear to be independent of bacterial infection, and that formalin-killed P. acnes failed to stimulate inflammation of cultured skin cells, [3] cast some doubt about the role of P. acnes in acne. Instead, these findings suggest that the accumulation of P. acnes in blocked pilosebaceous follicles may occur subsequent to the pilosebaceous obstruction, and may play a *secondary* rather than a primary role in the pathophysiology of acneform lesions. What, then, are the factors that cause the blockage of the pilosebaceous follicles in acne?

"You do not really understand something unless you can explain it to your grandmother."

-Albert Einstein

2. PHYSIOLOGY OF NORMAL FOLLICULAR DESQUAMATION: MAINTENANCE OF FOLLICULAR PATENCY

Pathology confirms that the comedonal follicular plugs consist of multiple layers of stratum corneum, with loss of a patent follicular lumen. It is believed that follicles plugged by stratum corneum may be the basis of acneform lesions. The plugged follicles interfere with normal function and drainage of sebum to the skin surface, and promote stasis and accumulation of P. acnes and its by-products in the sebaceous glands. In order to understand the pathophysiology of plugged pilosebaceous follicles, it is important to firstly understand the normal physiology of follicular desquamation and what maintains follicular patency in normal follicles.

The normal physiology of the hair follicle includes addition of new cells at the base of the follicular epidermis through basal cell proliferation. These basal cells differentiate into follicular keratinocytes, which eventually mature into stratum corneum cells. As a new cell is added to the stratum

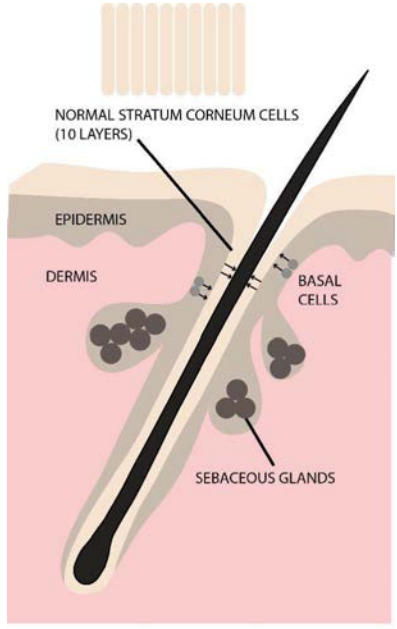

FIGURE 1: NORMAL HAIR FOLLICLE

Figure 1 shows a normal hair follicle with patent follicular passage for drainage of sebum from the sebaceous glands. The hair follicle is lined, usually by ten layers of stratum corneum, which is replaced by addition of new stratum corneum cells through proliferation of basal cells. Homeostasis is maintained by removal of old stratum corneum cells by the process of desquamation.

corneum from within, the old stratum corneum cell is sloughed off or removed from the surface by a process of desquamation. Normal physiological desquamation of the stratum corneum cells parallel the rate of basal cell proliferation. To maintain the patency of normal follicles, there is a balance between addition of new cells (proliferation) and loss of old stratum corneum cells (desquamation).

The process of stratum corneum desquamation involves digestion of the desmosomal cadherins, which are adhesive proteins responsible for intercellular adhesion of the stratum corneum cells. In desquamation, digestion of the desmosomal cadherins is achieved by proteolytic enzymes. The major proteolytic enzyme involved in the desquamation process is stratum corneum chymotryptic enzyme, a chymotrypsin-like proteinase. [4-6] This 25 kDa proteinase is active at pH 5.5, may be activated by proprionic acid released by P. acnes. [7] The proprionic acid lowers the follicular pH, resulting in activation of stratum corneum chymotryptic enzyme, followed by desquamation and removal of the top layers of stratum corneum in the hair follicle. Removal of the top layers of stratum corneum is necessary to maintain follicular patency in normal follicles.

Another enzyme believed to be involved in stratum corneum desquamation is kallikrein-related peptidase-8 (KLK-8). This is an active serine protease in human epidermis, and has considerable activity at pH 5.0. [6] This enzyme appears to have biphasic activity at both pH 8.5 and pH 5.0. [8] KLK-8 activity was observed to be enhanced by calcium and

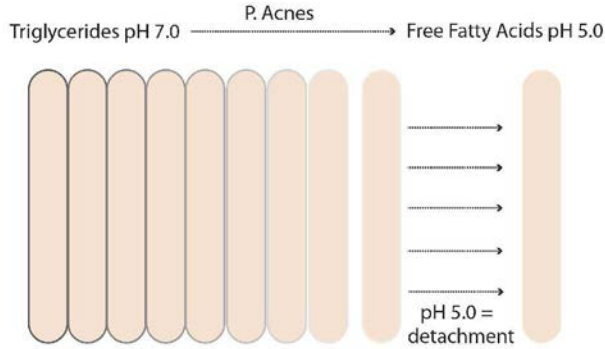

FIGURE 2: THE ROLE OF P. ACNES IN THE DETACHMENT OF STRATUM CORNEUM LAYERS

Figure 2 shows the role of P. acnes in providing the pH change (pH 5.0 – 5.5) necessary to activate desquamating enzymes (stratum corneum chymotryptic enzyme, pH 5.5, and kallikrein-related peptidase 8, pH 5.0) for removal of surface layers of stratum corneum cells necessary for follicular patency.

magnesium ions and attenuated by zinc ions. KLK5 and lysyl endopeptidase have been found to activate latent pro-KLK-8. As mentioned previously, proprionic acid (pH 5.0) secreted by P.acnes is beneficial for the activation of KLK-8 (pH 5.0), with important roles in desquamation and maintenance of follicular patency. Thus, preparations containing zinc, and other products which promote a pH environment other than pH 5.0 - pH 5.5, may interfere with normal desquamation and promote follicular plugging.

"*Every really new idea looks crazy at first*"

-Alfred North Whitehead

3. PATHOPHYSIOLOGY OF COMEDONES AND PLUGGED FOLLICLES IN ACNE

In acne, the follicles are often filled with a plug (comedone) consisting of many layers of voluminous stratum corneum. The pathophysiology of follicular plugging in acne can be the result of the following:

a. Over-hydration of the stratum corneum: This may be due to the use of moisturizers, conditioners in the shampoo, creams, lotions, oils, petrolatum, ointments, mousse in hair products, and moisturizers in make-up. Over-hydration of the stratum corneum causes the stratum corneal cells to swell and occupy more volume, thereby contributing to the follicular plug or comedone.

b. Decreased P. acnes population: The swelling of the stratum corneal cells decreases the space for growth of P. acnes. Since P. acnes function in stratum corneum desquamation, the depletion of the P. acnes population in

the hair follicle decreases the process of desquamation, and promotes comedone formation. The aggravating effect of anti-bacterial agents such as topical benzoyl peroxide products is shown by the formation of abnormally large comedones associated with the use of topical benzoyl peroxide preparations.

c. Miscellaneous factors contributing to decreased desquamation of stratum corneum may result in retention of increased layers of stratum corneum. Thus, factors that contribute to decreased activity of stratum corneum chymotryptic enzyme (SCCE) and kallikrein-related peptidase-8 (KLK-8) may also contribute to the formation of acne. These factors include disturbance of the normal optimal pH for activation of desquamating enzymes (between pH 5.0 – 5.5), and the presence of zinc ions which decrease the activity of KLK-8, may be expected to interfere with normal desquamation of the stratum corneum and promote follicular plugging and comedonal formation.

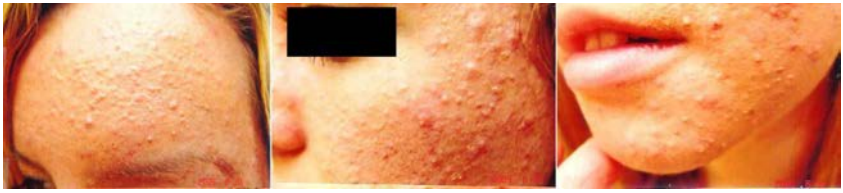

Figure 3: Observe the large comedones with the use of benzoyl peroxide topical preparations. Note the absence of pustules which are benefited by the use of benzoyl peroxide gel.

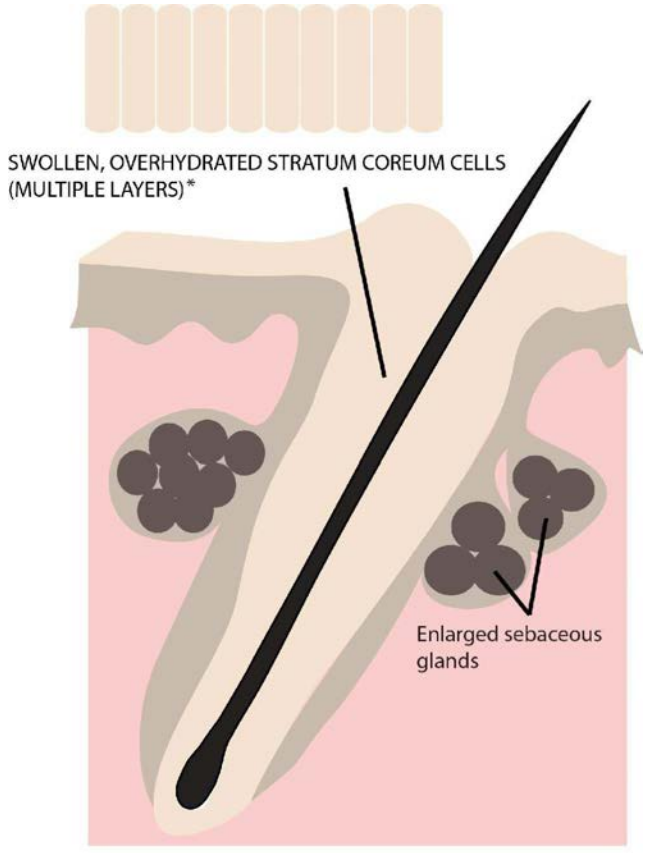

FIGURE 4: CLOGGED FOLLICLE (COMEDONE)

Figure 4 shows the effect of using conditioners, hair products, moisturizers, make- up and sunscreens with hydrating properties which cause the stratum corneum to swell and increase in volume, thus encroaching on the follicular space between the stratum corneum cells. The swollen stratum corneum cells form one type of comedone (follicular plug). The follicular plugs block the drainage of the sebum from the sebaceous glands as well prevent the removal of excess P. acnes from the follicle. The enlarged sebaceous glands leak both sebum and P. acnes into the perifollicular tissues, which induce the accumulation of neutrophils, resulting in the formation of acneform pustules and abscesses.

**Products that contribute to this type of clogged follicle:*
Conditioners, Hair products, (sprays, mousse, hair gels, styling wax), moisturizers, makeup, sunscreens, creams, lotions, oils, ointments.

"The most important thing in science is not so much to obtain new facts, but to discover new ways of thinking about them."

-William Lawrence Bragg

4. PROPRONIBACTERIUM ACNES: FRIEND OR FOE

In normal pilosebaceous follicles, the bacteria P. acnes assists in maintaining a patent follicular lumen by promoting the activity of the stratum corneum chymotryptic enzyme (SCCE) found in human sebaceous follicles. [5,6] Proprionibacterium acnes helps lower the follicular pH through secretion of proprionic acid and free fatty acids. In disease states, follicular plugging, for example from the use of moisturizers, lead to swollen stratum corneum cells, with narrowing or obliteration of the follicular space usually occupied by P. acnes. This leads to a depletion of P. acnes in the upper follicular passage. In addition, depletion of P. acnes population may also occur because of the use of anti-bacterial agents. The depleted P. acnes population in the upper follicular lumen results in loss of ability to maintain the follicular pH necessary for the optimal activity of the desquamating enzymes (SCCE and KLK-8), thus promoting comedone formation, and subsequent acne development.

Studies show that follicles from healthy skin with open follicular passages were exclusively colonized by P. acnes, whereas the follicular microbiota of acne patients were observed to include other bacteria such as Staphylococcus epidermidis and several other minor species. [9] The authors used 5700 amplified and cloned 16S rRNA genes to determine the microbial diversity in follicles from acne patients, healthy individuals and from the superficial skin of acne patients. [9] Their findings confirm the preference of P. acnes for the microaerophilic environment of normal healthy follicles. It is believed that the P. acnes function to produce proprionic acid [7] resulting in an ideal pH of 5.0 that activates the desquamating activity of SCCE [6] and KLK-8 [8]. This then causes physiological desquamation of the superficial layers of follicular stratum corneum. Thus, P. acnes play an extremely important role in maintaining normal follicular patency, and preventing acne development.

Pathophysiology of Inflammatory Acne

Acne may be said to be “like a clogged sink” – the blockage resulting in lack of drainage and resultant accumulation of micro-organisms including bacteria and fungi that are known to cause inflammation. It is believed that had the sink not become clogged, the overgrowth of bacteria and fungi in the static water would not then be an issue.

The clogged sink analogy represents the situation in acne, which is due to plugging of the outflow tract of the hair follicles. Because the outflow tract is plugged, sebum from the sebaceous glands cannot drain to the surface. The failure of the oil glands to drain results in over-filled sebaceous glands containing an over-abundance of bacteria. Eventually, the bacterial by-products leak into the surrounding dermis because of defects in the stretched sebaceous basement membranes. The chemotactic properties of the bacterial by-products result in neutrophil infiltration and acneform abscess formation.

Role of inflammation and chemotactic factors in acne

The observation of inflammatory cells like neutrophils, and

sometimes monocytes, in which are found in bacteria, and contain N-formyl-methionine-leucine-phenylalanine or fMLP peptides, (b) chemokines which are a special class of cytokines, such as IL-8 (interleukin-8), RANTES, TNFα (tumor necrosis factor-alpha), and (c) complement C3a and C5a, secreted from the activation of the classical pathway, alternative pathway and lectin-induced pathways. Additional factors include leukotrienes, in particular LTB4 (leukotriene B4) which amplifies the effect of formylated peptides on neutrophil chemotaxis.

TABLE 1: NEUTROPHIL CHEMOTACTIC MOLECULES IN ACNE

1. **fLMP peptides (bacteria)**
2. **Interleukin-8 (IL-8)**
3. **RANTES**
4. **TNF-a**
5. **Complement C3a and c5a**
6. **Leukotrienes (LTB4)**

Table 1 summarizes the chemotactic factors that may be functioning to attract neutrophils into pustules and abscesses in acne vulgaris.

Role of Proprionibacterium acnes as an instigator of acneform pustules

Early investigators of acneform lesions suggest that neutrophils may be the early instigators of acneform pustules. [1,2] The knowledge that formylated peptides in the bacterial cell membrane (fMLP) are potent chemotactic agents for neutrophils has led to incrimination of the commensal bacterium, P. acnes, as an instigator of acneform pustules. This view has been supported by in-vitro studies demonstrating release of lysosomal hydrolase by neutrophils in response to P. acnes, with enhancement by sera from inflammatory acne patients. [10] The authors also demonstrated formation of antibodies against P. acnes cell wall carbohydrate in patients with nodulocystic acne (11] as well as activation of complement (alternative pathway) by P. acnes cell wall carbohydrate. [12]

A study has shown that follicles from healthy skin of acne-free patients were exclusively colonized by P. acnes, whereas the follicular microbiota of acne patients included, in addition, Staphylococcus epidermidis and several other minor species. [9] This suggests that when the flow of sebum and P. acnes to the skin surface is disrupted, such as by follicular plugging, accumulation of a number of bacteria occur in the static environment. These accumulated bacteria produce by-products, including formylated peptides which are chemotactic to neutrophils, as well as tissue-degrading enzymes. Proteomic studies of secreted proteins from P. acnes [13] have identified several proteins possessing tissue-degrading activities. These include glycoside hydrolases with similarities to endoglycoceramidase, such as β-N-acetylglucosaminidase and muramidase, esterases such as lysophospholipase and triacylglycerol lipase, as well as several proteases. The tissue-degrading enzymes are capable of digesting cell membranes of the sebaceous glands, causing disruption of the pilosebaceous apparatus and instigating the formation of acneform abscesses. The P. acnes then spill into the surrounding tissues, and further stimulate neutrophil chemotaxis through the presence of formylated peptides in the bacterial cell membrane. These formylated peptides, in turn, trigger Toll receptors-dependent cytokine responses [14,15]. The authors found that transfection of Toll-like receptor-2 (TLR2) into a non-responsive cell line was sufficient for NF-kB activation, and observed the expression of TLR2 on the cell surface of macrophages

surrounding pilosebaceous follicles in acne patients. This response by TLR-2 in acne patients may be tissue-specific since in the liver, it was found that TLR2 recognizes the ligands, such as peptidoglycan and lipotechoic acid from bacterial cell membranes. It is of interest that P. acnes priming was observed to sensitize the cells to skin-specific Toll-like receptor-4 (TLR4) but not the liver-specific, TLR2. [16]

The current evidence points to the secondary role of P. acnes in the pathogenesis of acneform lesions. P. acnes appears to instigate inflammatory responses in follicles that are primarily plugged. In plugged follicles, the accumulation of P. acnes and subsequent inflammatory products promote neutrophil chemotaxis, with eventual development of pustules and abscess formation.

Antibiotic Resistant P. acnes

Although antibiotic resistant P. acnes have been reported, [17,18] these have not been a problem as long as the follicular pores are unplugged. The evolution of P. acnes with virulence genes tly and camp5, may explain the geographic and temporal dissemination of some “epidemic” clones [19]. It is possible that the use of topical antibacterial agents, including benzoyl peroxide, contributed to the development of resistant strains. In my experience antibiotic resistance is not a problem if benzoyl peroxide topical preparations are avoided. The use of topical antibacterial agents such as clindamycin should be restricted to focal treatment of pustules. Antibiotic-resistant P. acnes was an issue in 2001-2003, [17,18,20] but is thought not to be an important issue in recent years.

Possible Granulomatous Response Induced by P. acnes: Acne Fulminans

It is believed that in certain patients with severe acne associated with extreme scarring and granulomatous response, P. acnes may serve as an inducer for granulomatous hypersensitivity reactions in genetically predisposed individuals. The detection of P. acnes DNA in brochoalveolar lavage cells from patients with sarcoidosis [21] suggests the possibility that in genetically susceptible individuals, P. acnes may serve as an antigen inducing the scarring granulomatous response noted in this disease.

TABLE 2: MY ACNE TREATMENT PROTOCOL

1. Unplugging the plugged follicles
2. Control of pustules and abscesses
3. Skin care and special hygiene
4. Controlling Sebaceous Hyperplasia
5. Controlling Cystic Acne &
Treatment of residual scarring

"*There is no adequate defense, except stupidity, against the impact of a new idea*"

-Percy Williams Bridgman

5 TREATMENT PROTOCOL: UNPLUGGING THE FOLLICLES

Curcumin Gel

I have found curcumin gel to be helpful for acne in my practice. Curcumin gel is formulated with a pH of 5.0 to 5.2, which is used to promote desquamation of the follicular stratum corneum. This is most likely achieved by stimulating the activity of the desquamating enzymes (stratum corneum chymotryptic enzyme and kallikrein-related peptidase-8). Since curcumin has anti-photodamage properties, [22] the preparation is applied each morning following washing of the face with glycerin soap (or water alone if the skin feels dry). After washing and rinsing off with water, pat dry, and apply a small dab of curcumin gel, which is massaged into the skin with the fingers, spreading the gel thinly to cover as much skin as possible. When used under make-up or sunscreen, this layer of curcumin gel also serves to prevent clogging of the pores by make-up and sunscreen. For areas with scarring, I use a higher concentration preparation of curcumin gel. This is massaged into the scarred areas morning and night.

Retinoids

Apply retinoic acid gel 0.025% (Retin-A gel 0,025% or Tretinoin gel 0.025%) after washing the face with glycerin soap or water alone (if the skin feels dry). Because retinoids may be irritating and photosensitizing, they are used at bed-time.

After washing the face, wait 30 mins for the skin to dry out before applying the retinoic acid gel. When the skin is first allowed to dry, there is decreased penetration through the skin, and and retinoic acid gel is less irritating. Apply the gel thinly over the areas affected by acne while avoiding the corners of the eyes, nose and mouth. The retinoic acid gel 0.025% has a pH of 5.5 and helps desquamation of the stratum corneum by stimulating the activity of the stratum corneum chymotryptic enzyme.

High dose oral vitamin A

Patients with severe acne, particularly those with severe follicular plugging, may benefit from Kligman's regimen using high dose oral vitamin A. [23] Kligman observed that oral vitamin A at doses of 50,000 IU to100,000 IU daily was ineffective. However, he found that doses of 300,000 IU daily were highly effective for women, while men may require doses of up to 500,000 IU daily. Toxicity was reported to be limited to the skin and mucous membranes, presenting mainly as xerosis and cheilitis. Kligman considered the dangers of vitamin A toxicity to be exaggerated. In my practice, I have limited treatment to 300,000 IU for both sexes, with duration usually about 9 months. I also warn my younger female patients against becoming pregnant while on treatment.

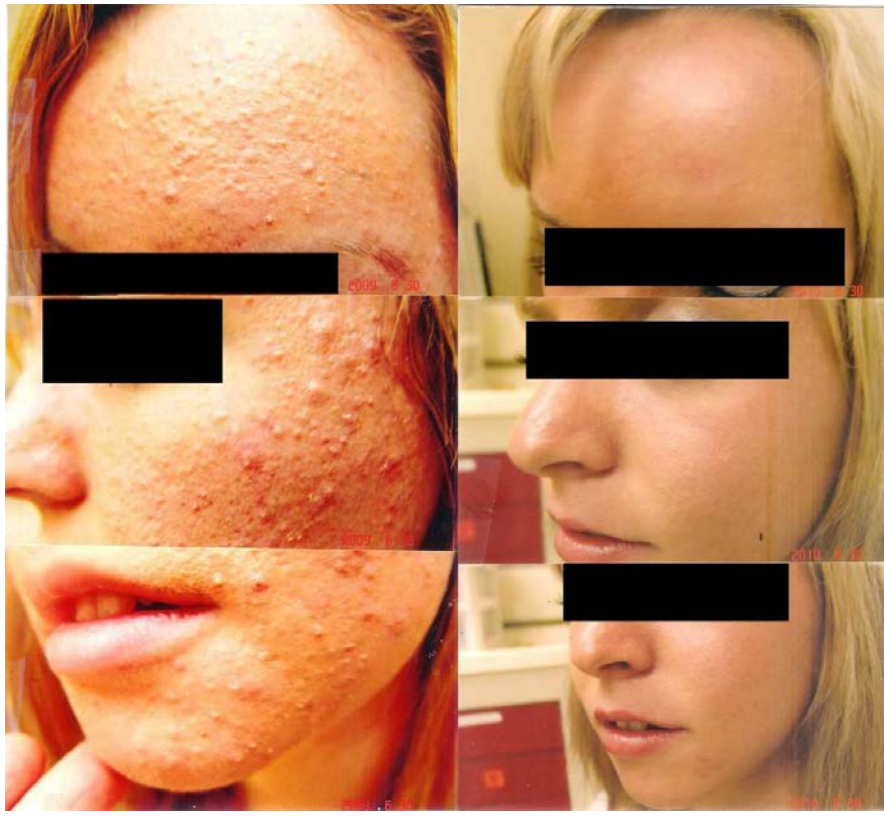

Figure 5 (left panels): Severe comedonal acne associated with the use of benzoyl peroxide gel. Note absence of pustules with presence of large comedones.

Figure 5 (right panels): Clearance of acne 12 months later with high dose oral vitamin A (300,000 IU daily for 9 months), curcumin gel in the mornings, and retinoic acid gel 0,025% at bed-time, oral doxycycline and lactose free diet.

"In the long run, there are no secrets in science. The Universe will not cooperate in a cover".

-Arthur C. Clark & Michael Kube-McDowell

6 TREATMENT PROTOCOL: CONTROLLING PUSTULES WITH ANTIBIOTICS

Pustules and abscesses resolve with the oral antibiotics, doxycycline or minocycline, and also with topical antibiotic, clindamycin (the use of which is limited for spot treatment of the pustules). It is best to avoid benzoyl peroxide-containing products which tend to deplete the P. acnes population. As mentioned above, depletion of the P. acnes population tend to interfere with activation of the stratum corneum chymotryptic enzyme necessary to maintain patency of the follicles by the desquamating activity of the enzyme. Unlike benzoyl peroxide which promotes an oxidative environment antagonistic to the survival of the microaerophilic P. acnes, clindamycin solution tends to shrink the pustules without changing the oxygen content of the follicular environment, and may be less damaging to intrafollicular P. acnes population.

The tetracycline family of antibiotics (doxycycline and minocycline) are protein synthesis inhibitors and tend to decrease oil production by inhibiting sebum production. This is beneficial for acne patients since increased oil production aggravates the acneform process. When the patient has fewer than two new pimples per week, it may be time to withdraw from oral antibiotic therapy.

"Nothing is too wonderful to be true if it is consistent with the laws of Nature"

-Michael Faraday

7 TREATMENT PROTOCOL: SKIN CARE & SPECIAL HYGIENE

The basic general principles of skin care in acne patients include avoidance of moisturizers, conditioners, creams and oils that cause the stratum corneum cells to swell and clog up the pores. The patient is advised to avoid conditioners in the shampoo and use baby shampoo instead. The patient is to wash with a mild glycerin soap, which does not contain oil, and to avoid creams, oils, lotions containing oil, ointments, mousse and oily hair products. In the event the patient chooses to wear make-up and sunscreen, plugging of the pores may be prevented if the patient applies a layer of curcumin gel under the make-up or sunscreen.

a. Glycerin soap.

Glycerin soap contains no oil, and is more gentle than regular soap. Since regular soap consists of a sodium salt of free fatty acid (usually palmitic or stearic acid), the sodium reacts with water and becomes sodium hydroxide

which gives the soap its cleansing properties. However, since sodium hydroxide is a strong alkali, it is also very irritating. This irritation is not seen with glycerin soap.

Acne is often associated with excess oil production, however the surface skin of acne patients is unexpectedly dry. As a result of blocked pores, the oil is trapped deep in the dermis and does not moisturize the surface skin. Thus, acne patients frequently complain of dry skin. Should the skin feel dry, the patient should avoid soap, and wash with tepid water alone. When the treatment takes effect and the pores become unplugged, the skin will become more oily. At this time, the patient may use soap more frequently. However, in the initial stages of the treatment, the skin will feel dry because most of the pores will still be blocked. During this period, the patient should tailor the washing with soap to the amount of oils capable of reaching the skin surface, and only use soap when the skin is oily, and water alone when the skin feels dry. In this way, over-washing does not occur and the skin will not become dry and cracked. Using external moisturizers may clog up the pores, and worsen the acne process.

b. Wash cloth recommendations:

It is better to use a fresh wash cloth to wash the face, since this provides better contact and cleaning potential, and removes oil and desquamated stratum corneum cells far better than the fingers. The wash cloth needs to be changed daily to avoid transfer of oils and pathogenic bacteria to the skin. Use the wash cloth gently on the skin and avoid scrubbing.

c. Avoid using conditioners in the shampoo:

Conditioners in the shampoo are moisturizers, which cause overhydration of the stratum corneum cells, and promote follicular plugging. Baby shampoo is a shampoo without conditioners.. Avoid clear shampoos containing oils such as eucalyptus oil, or lavender oil, since the oily products may be comedogenic from their oil content. Conditioners and moisturizing products are frequently responsible for multiple comedones over the forehead

and temple. In addition, the eucalyptus oil and lavender oil, may have anti-bacterial properties, and may aggravate acne by depleting the P. acnes population within the hair follicles.

d. Change pillow cases frequently:

Pillow cases should be changed every other day so that the accumulated oils in the pillow cases do not contact the skin with their comedogenic effect. An alternative is placing a freshly washed towel on top of the pillow, changing this every night, or every other night. Bed sheets should also be changed frequently if the patient has acne over his back. Daily changes of T shirts are also recommended for the same reason.

"*Scientists are to journalists what rats are to scientists.*"

-Victor Cohn

8 TREATMENT PROTOCOL: SEBACEOUS HYPERPLASIA AND LACTOSE INTOLERANCE

An important issue that is often overlooked in acne is the presence of enlarged sebaceous glands or sebaceous hyperplasia. These enlarged sebaceous glands constrict the pilosebaceous follicles from the outside, thus compromising drainage of sebum from the sebaceous glands to the skin surface, leading to aggravation of pre-existing acne.

In my experience, the most common cause of sebaceous hyperplasia is underlying lactose intolerance. Most human populations are not able to digest lactose because the ability to secrete lactase is lost after the age of 5 years. The undigested lactose spills into the colon and raises the osmotic pressure, making it difficult for the colonic bacteria to survive. The dead colonic bacteria release lipopolysaccharides (LPS), which stimulate Toll receptors through binding to MD-2.[26] MD-2 is associated with TLR-4 (Toll-like receptor-4) on the cell surface and enables TLR4 to respond to LPS [26].

LPS behaves like a superantigen in activating T lymphocytes to secrete large amounts of cytokines, such as TNFα, and growth factors such as transforming growth factor-α (TGFα). [27] The TGFα stimulates the formation of skin tags, and warty growths on the skin, [28] as well as enlargement of sebaceous glands or sebaceous hyperplasia.

The cascade of events as detailed above in lactose intolerant individuals result in changes in the skin such as sebaceous hyperplasia and skin tags. Avoidance of dairy products (milk, cheese, ice-cream, yogurt, pizza, pastry, cream, cream soups, Ranch dressings and chocolates among others) often lead to significant improvement in sebaceous hyperplasia usually after 3-6 months.

"*Medicine, the only professor that labors incessantly to destroy the reason for its existence*".

-James Bryce

9 TREATMENT PROTOCOL: CONTROLLING CYSTIC ACNE & TREATMENT OF RESIDUAL SCARRING

Acne conglobata (cystic acne) is a form of acne that is associated with large comedones and multiple cystic abcesses. The lesions often heal with severe scarring. Although treatment is the same as for regular acne, I have found, in addition, high dose oral vitamin A23 (300,000 IU (for at least 9 months) is an excellent treatment for improvement of cystic acne. In the past Accutane was used, but with side-effects including psychosis, and birth defects. The human metabolic systems predominantly prefer to use molecules which are oriented in an orientation called the "trans" orientation. "Cis" and "trans" refer to the way the molecules are oriented in space (left or right handed). Accutane (13 cis retinoic acid), is a “cis” molecule. It is not easily metabolized by human cells, and accumulates to toxic levels. On the other hand, Vitamin A (all-trans retinol) is a “trans” molecule, which is capable of being metabolized by human cells, with no apparent toxicity until doses of at least 20,000,000 IU are administered.

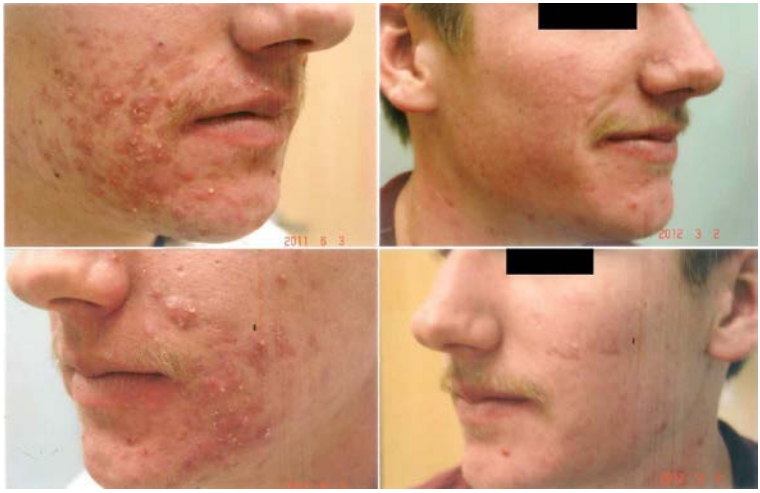

Figure 6 left panels: Severe acne conglobata with failure to respond to standard therapy.

Figure 6 right panels: Acne conglobata: much improved after 9 months of high dose oral vitamin A, oral doxycycline 100 mg twice daily, curcumin gel during the day, and retinoic acid gel 0.025% at night. He used glycerin soap, baby shampoo and was on a lactose free diet.

For this reason, Accutane is currently avoided by many dermatologists, and high dose oral vitamin A remains a viable option. However, as a precautionary measure, female patients should be counseled with regard to avoiding pregnancy while taking oral vitamin A, and be cognizant of the potential risk of fetal abnormalities even with the use of oral vitamin A, at doses higher than recommended daily requirements.

The high dose oral vitamin A improves desquamation of the stratum corneum follicular plugs from the granular layer outwards towards the surface, and helps unplugging of the plugged follicles in cystic acne. In addition, in my experience, the use of curcumin gel is also extremely helpful in the treatment of cystic acne, with the regular strength curcumin gel to unplug the pores, and the higher strength curcumin gel for the treatment of acne scars.

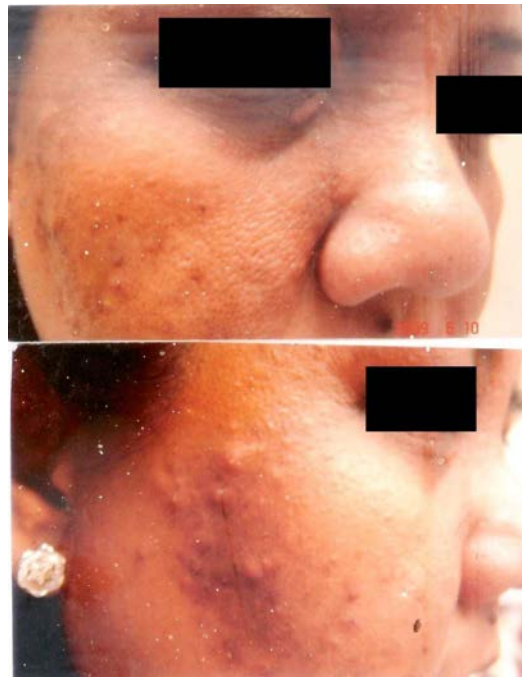

Figure 7: Note the dark circles around the eyes, which are a common feature in lactose intolerance. Also note the enlarged pores around the paranasal cheeks, which are characteristic of lactose intolerance. Finally, note the deep cysts due to sebaceous hyperplasia combined with plugged follicles. These tend to heal with scarring.

It is also important to avoid conditioners in the shampoo, mousse, Vaseline and products with moisturizing properties since they tend to clog up the pores. I recommend the use of glycerin soap for cleansing, while avoiding moisturizers. The application of regular strength curcumin gel under sunscreens is helpful in order to prevent further clogging of the pores. If large pores or sebaceous hyperplasia are present, these tend to improve with a strict lactose-free diet. The sebaceous hyperplasia in association with plugged follicles may result in deep cysts, which tend to heal with scarring.

A lactose free diet is an essentially dairy free diet free from cow's milk and milk products (milk, cheese, ice-cream, yogurt, pizza, batter, cakes, cream soups, all kinds of creams, creamy butter, sour cream, Ranch dressing and chocolates, among others). However, patients should be aware that lactose is often added as a filler to seasonings, such as ground pepper, garlic, and taco seasoning among others, and to powdered drinks. In addition, lactose is also used as a base for making tablets.

Miscellaneous types of acne include acne due to intake or over secretion of testosterone or androgenic hormones, including stress, oral contraceptives, acne from the use of lithium prescribed for bipolar disease, and acne from iodides, bromides and agent orange. These lesions can be treated as regular acne, together with removal of the additional aggravating factors.

The formation of residual scars is a common observation following resolution of acneform pustules and abscesses, with more scarring from the large cytic abscesses than from the smaller pustules.

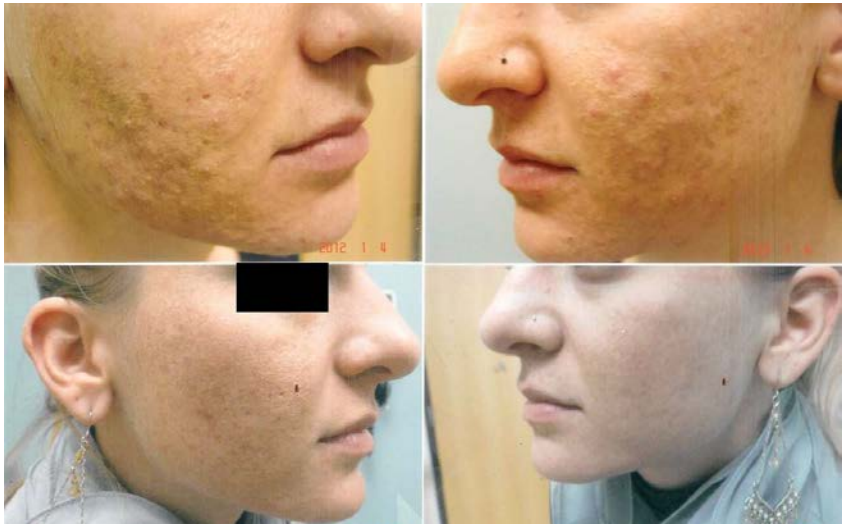

Figure 8 top panels: Severe acne with residual scarring prior to using curcumin gel.

Figure 8 bottom panels: Improvement of scars with extra-strength curcumin gel applied twice daily.

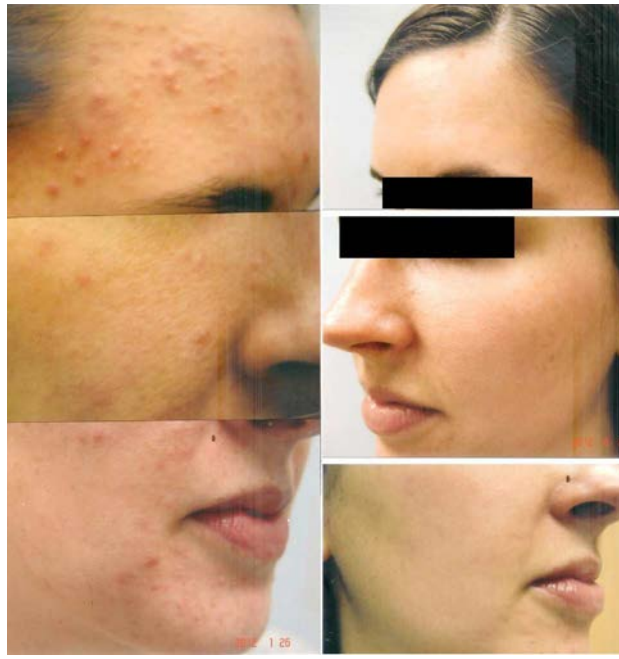

Figure 9 left panels: Patient with comedones over the temples (aggravated by conditioners in the shampoo), cheeks and chin (aggravated by moisturizers, sunscreens and make-up.

Figure 9 right panels: Improved with oral vitamin A, retinoic acid gel 0.025% at bed-time, curcumin gel during the day, oral doxycycline, and avoidance of conditioners, make-up and moisturizers. Sunscreens were used over the curcumin gel to prevent clogging of the pores.. Residual scarring was also benefited by the curcumin gel.

In my practice, I have found that early treatment and prevention of scars may be achieved with the use of curcumin gel, which has been shown to heal surgical scars [24] and burns [25] with minimal scarring. [24] Scar tissue formation can be divided into two stages. The initial phase of fibroblast proliferation is reversible, while the later phase of myofibroblast proliferation produces hypertrophic scarring, which is much harder to reverse. Scarring is best treated with a higher concentration preparation of curcumin gel applied at least twice daily to the scarred areas, with the gel massaged into the skin with the fingers.

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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.

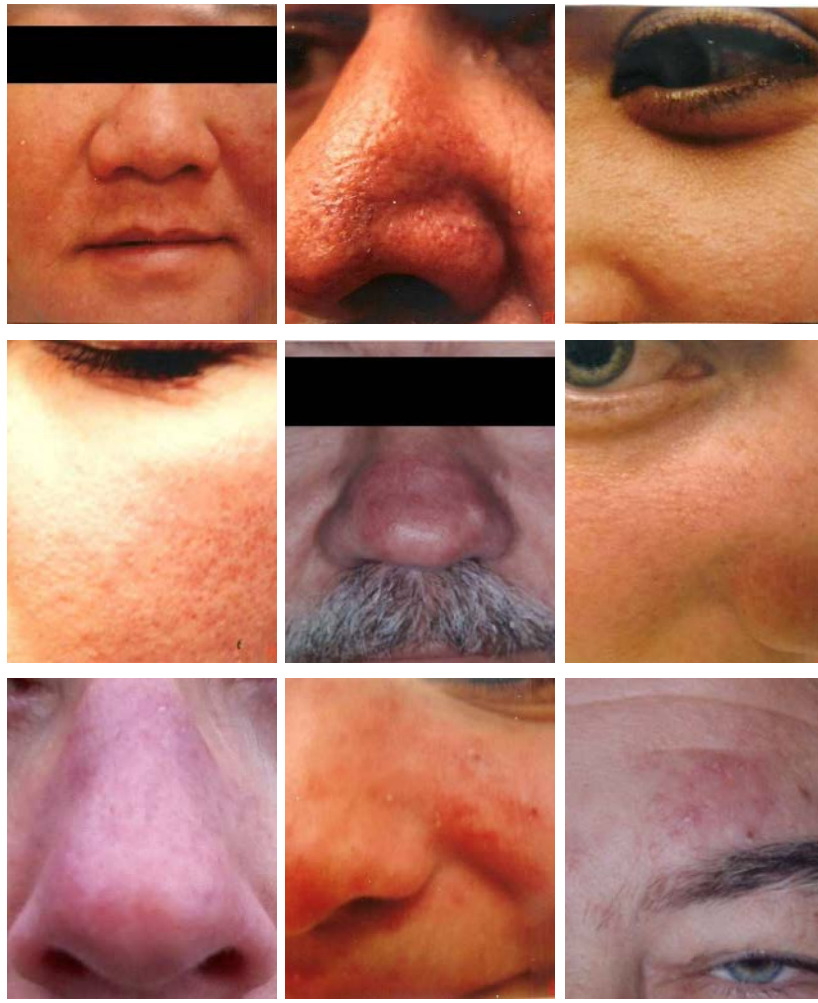

Figure 1: Various manifestations of Rosacea symptoms

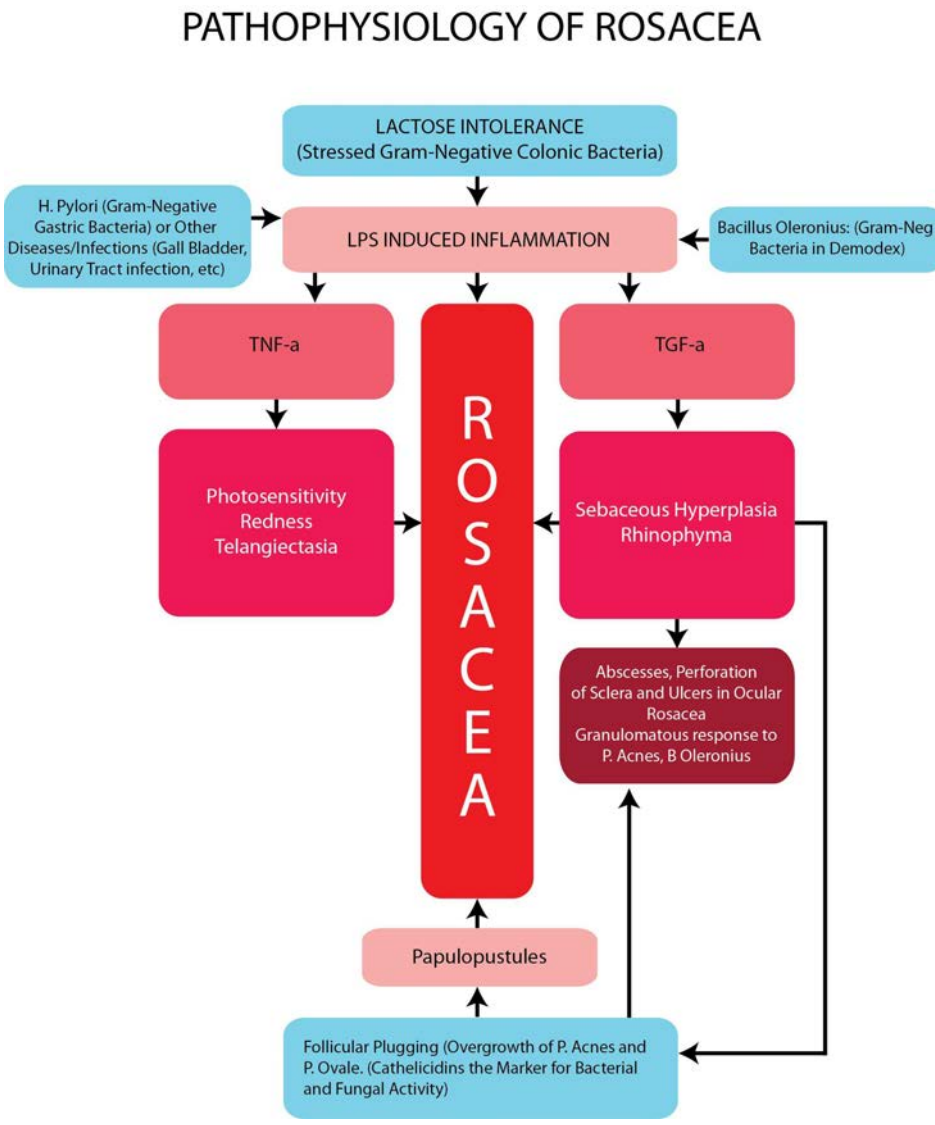

Figure 2: Pathophysiology of Rosacea

"*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]

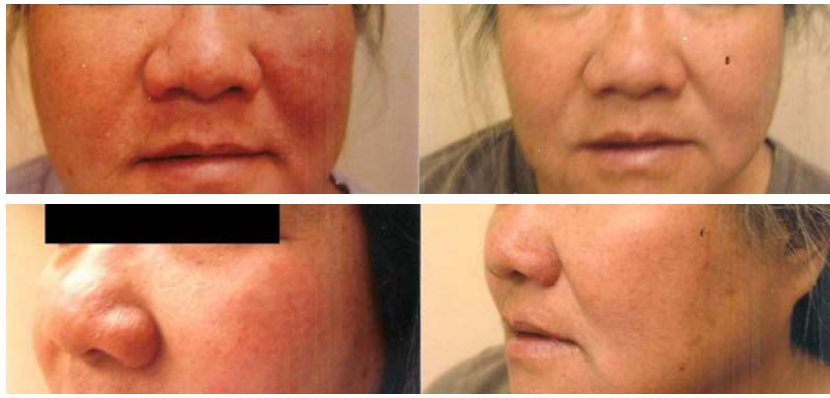

Figure 3: Patient showing erythema and sebaceous hyperplasia (left panels), both of which improved after 6 months (right panels) with a lactose-free diet, curcumin gel and oral minocycline.

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.

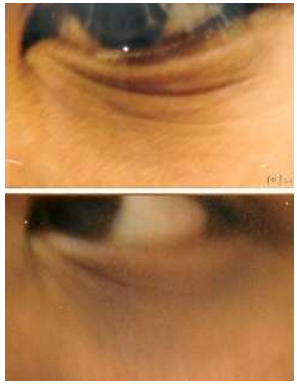

Figure 4: Teenager with prominent eyelids associated with lactose intolerance (upper panel). Note improvement after 6 months on a lactose-free diet and curcumin gel (lower panel).

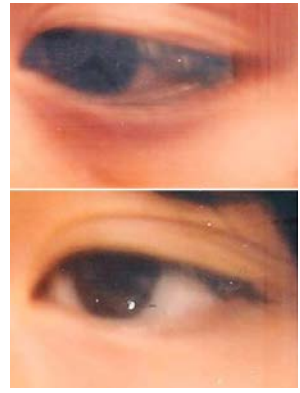

Figure 5 shows a 9 year old patient with dark circles around the eyes and mild rosacea with early enlargement of sebaceous glands (upper panel). Note improvement after 6 months on a lactose-free diet (lower panel).

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.

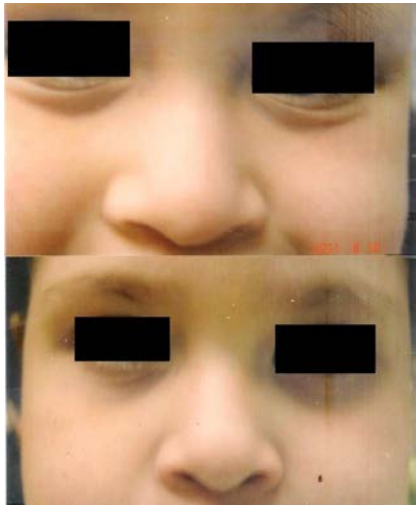

Figure 6: Two-year old child with heavy eyelids associated with lactose intolerance. Note early rosacea and early enlarged sebaceous glands (upper panel), with improvement after 3 months of lactose curtailment (lower panel). The patient was taking calcium and vitamin D supplements.

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).

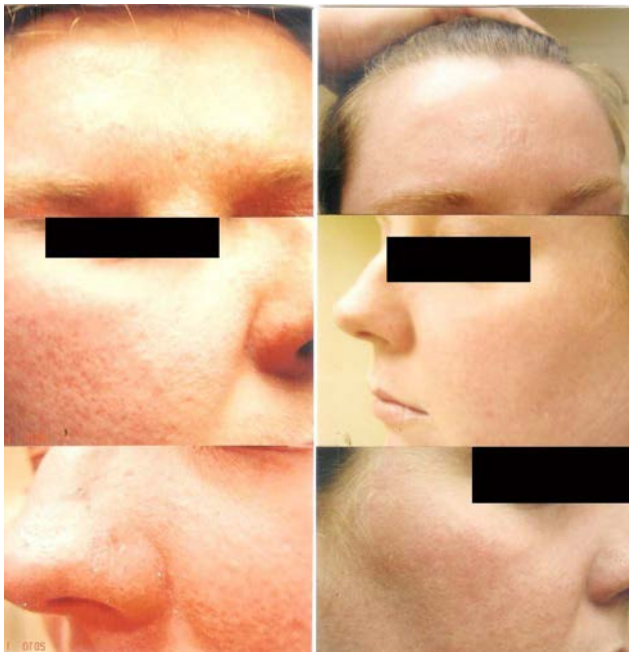

Figure 8: The erythematous rosacea associated with sebaceous hyperplasia is also benefited by curcumin gel applied underneath a layer of sunscreen. The patient was also put on a lactose-free diet, which was responsible for the improvement in sebaceous hyperplasia as well as decreased photosensitivity 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.

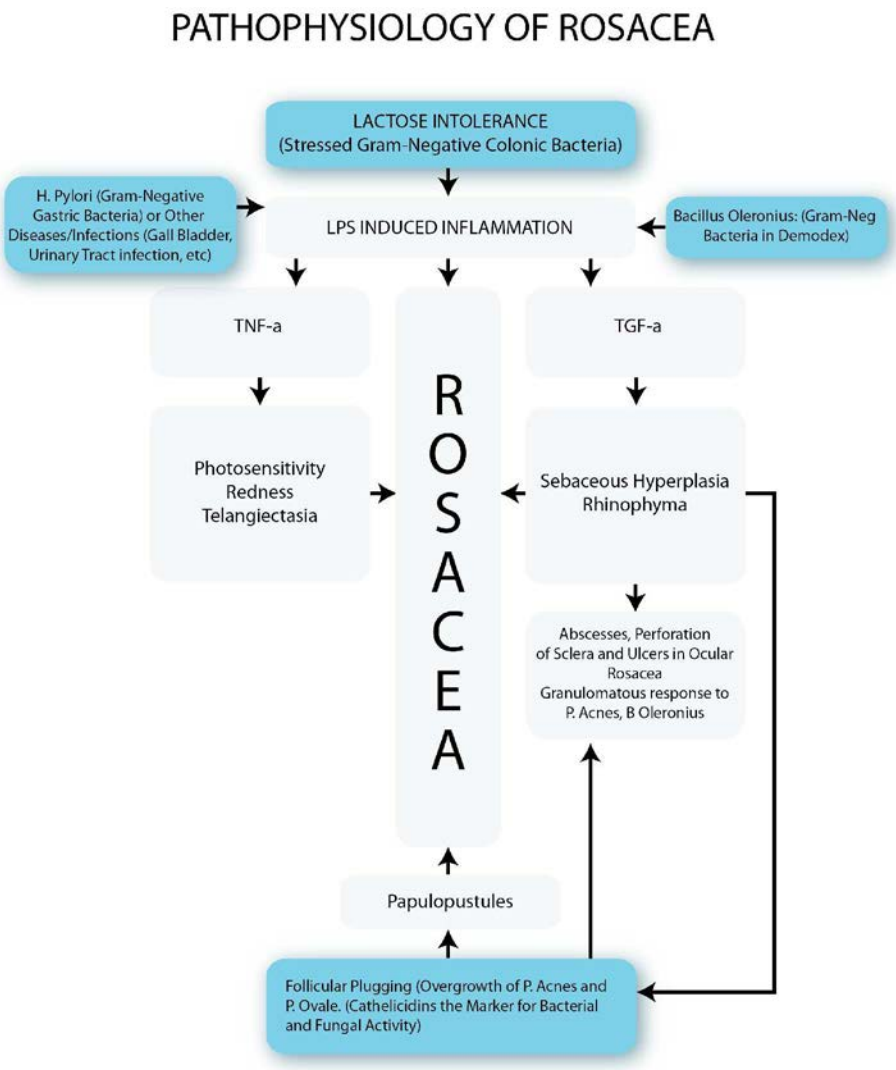

Figure 9: Causative Factors that Aggravate Rosacea

"*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

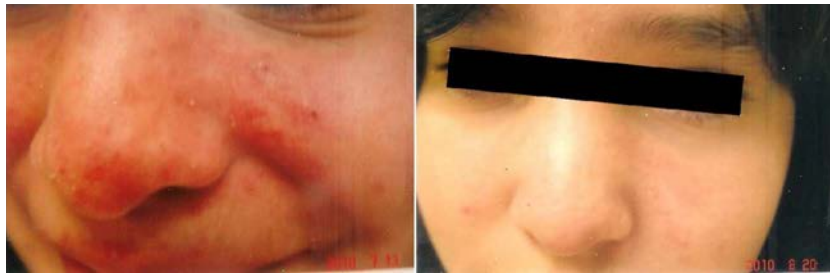

Figure 10: Superinfection of the skin by pathogenic gram positive bacteria such as Staphylococcus aureus and Streptococcal sp should be considered in patients with a history of worsening rosacea with pustules. The pustules and skin should be swabbed for bacterial culture and sensitivity, and the antibiotic 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]

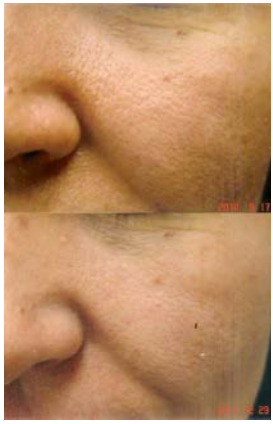

Figure 11: Shows a rosacea patient with mild erythema but prominent sebaceous hyperplasia which improved after 3 months (bottom panel) with a lactose-free diet and curcumin gel.

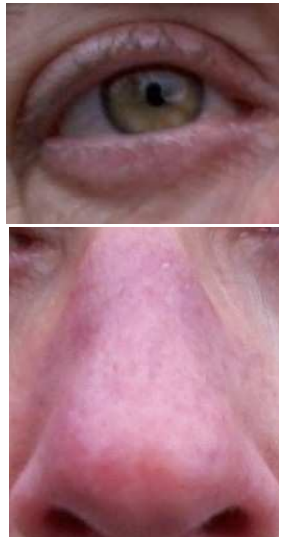

Figure 12 upper and lower panels Shows a patient with rosacea aggravated by chronic nasal allergies. The condition is aggravated also by constant use of topical steroid sprays.

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.

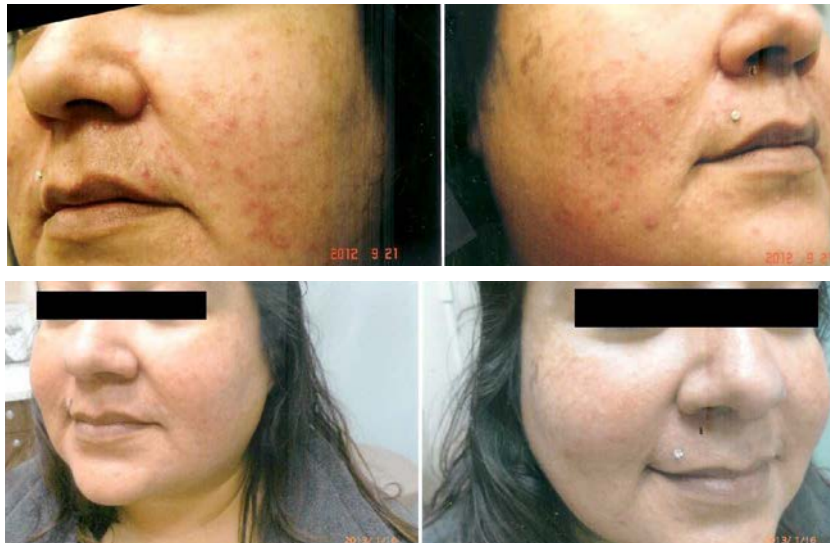

Figure 13: Rosacea with pustules aggravated by lactose intolerance (major) and by sinus infections (minor). Improvement was achieved with adequatae treatment of her sinus infection, lactose-free diet, oral doxycycline and curcumin gel.

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.

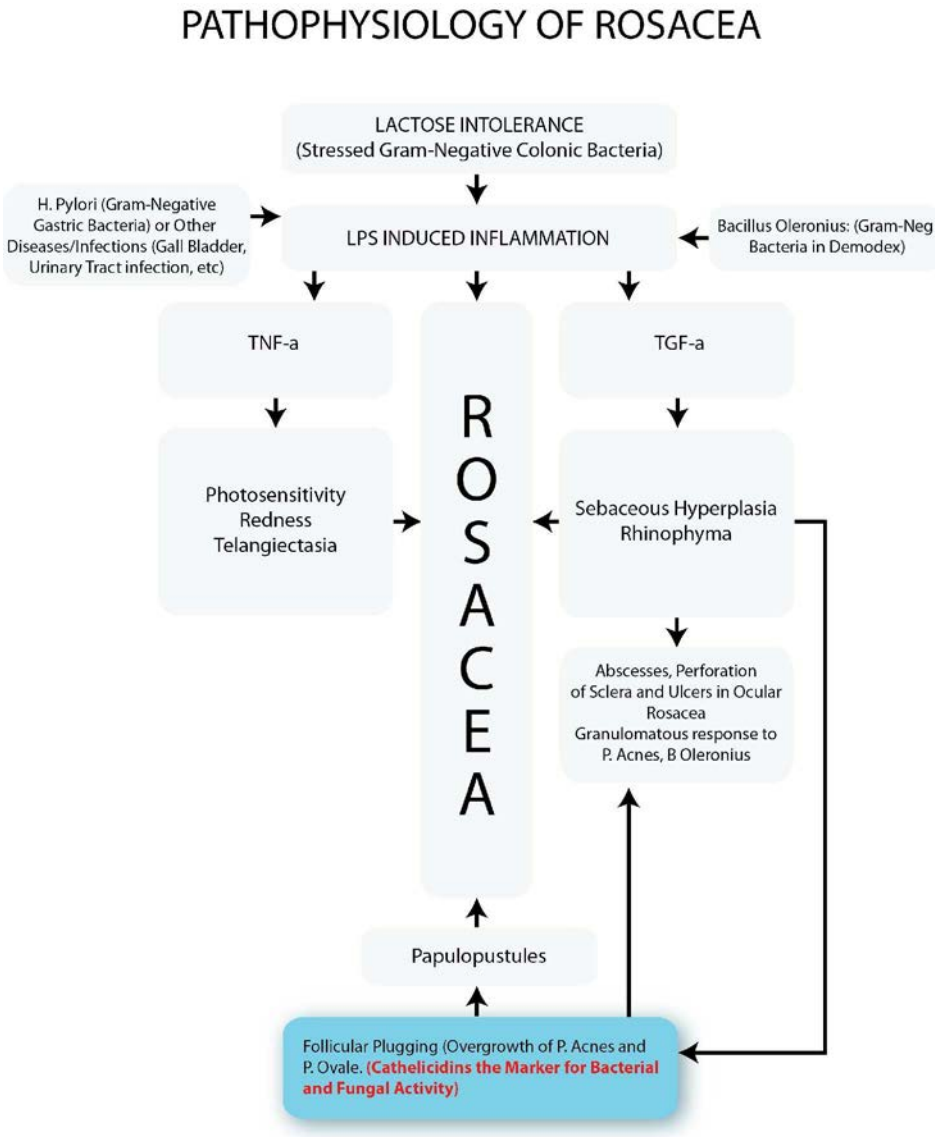

Figure 14: Cathelicidins, one of the causative factors in aggravation of Rosacea

"*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

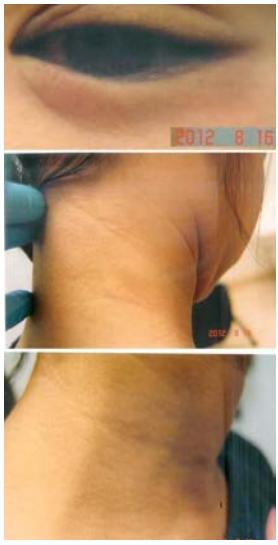

Figure 15: Ten year old patient with heavy eyelids (upper panel) and early acanthosis nigricans affecting the skin of the neck, which was both thickened (middle panel) and hyperpigmented (bottom panel).

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.

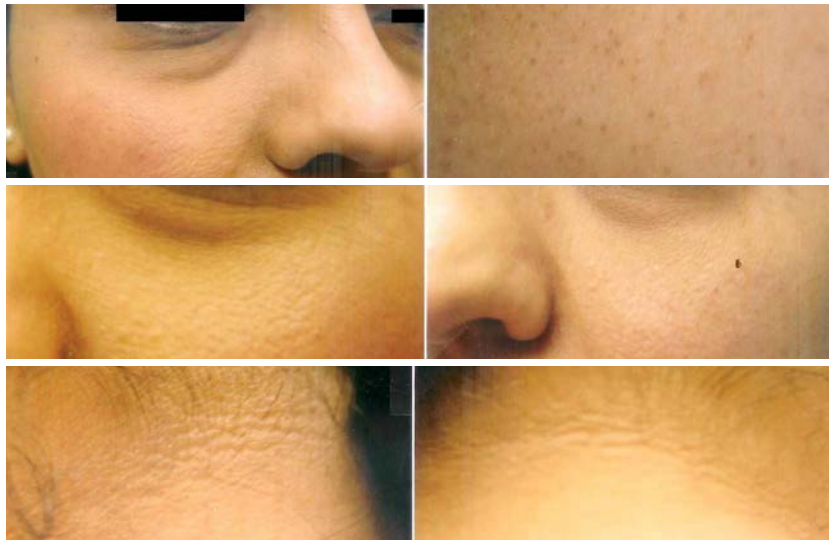

Figure 16: Patient with lactose intolerance with rosacea, sebaceous hyperplasia, heavy eyelids (upper left, and acanthosis nigricans affecting the neck (bottom left) associated with early skin tags of the neck (upper right). Improvement in the neck after 6 months on a lactose-free diet, was associated 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

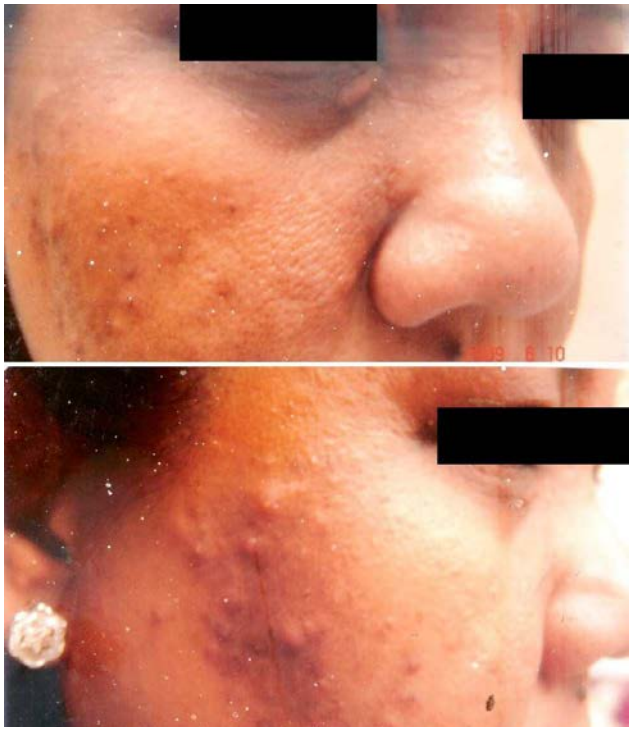

Figure 17: Patient with lactose intolerance with dark circles around her eyes, sebaceous hyperplasia, cysts around her eyes, and deep scarring acneform abscesses over her preauricular cheeks from the use of moisturizers and conditioners in the shampoo.

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).

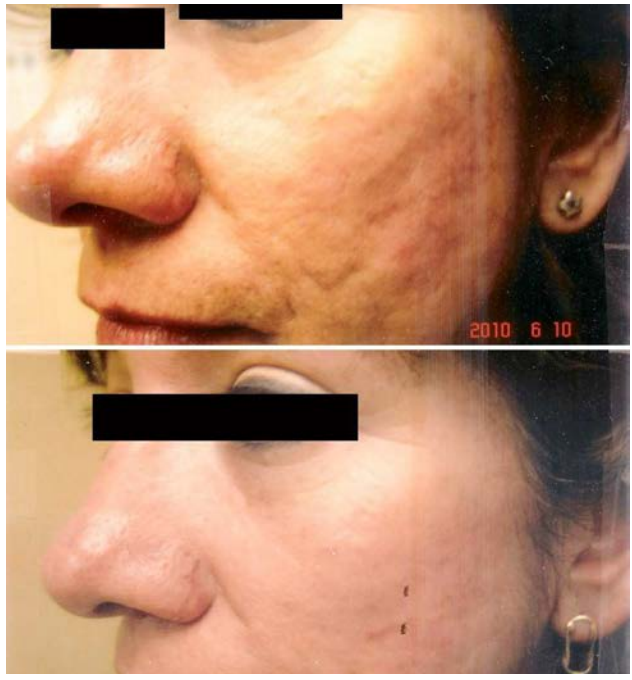

Figure 18: Improvement of melasma is seen after 6 months with a lactose-free diet, assisted by the curcumin gel (applied all over) and localized application of sunscreen over the curcumin gel in the hyperpigmented areas. Note improvement of both the sebaceous hyperplasia and melasma.

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.

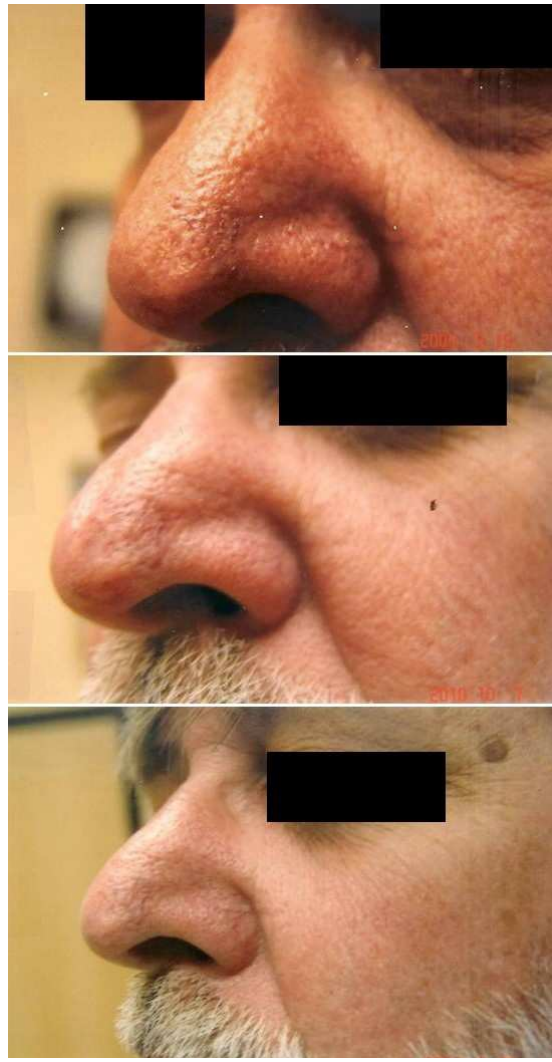

Figure 19: Erythematous rosacea with sebaceous hyperplasia may be associated with increased TNFα associated with lactose intolerance, and patients will benefit from strict curtailment of lactose in the diet.Patient with erythematous rosacea with sebaceous hyperplasia (top panel), improved after 6 months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

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Madalene Heng, MD, FRACP, FACD, FAAD, is currently Clinical Professor of Medicine/Dermatology at UCLA School of Medicine. She was in full-time academia for 25 years, including many years as Chief, Division of Dermatology, UCLA-San Fernando Valley Medicine Program, where she advanced to Professor of Medicine/Dermatology at UCLA.

Currently in private practice in Camarillo, California, she continues to teach trainees in UCLA system, and physicians within the country and abroad. She is also a reviewer for many national and international journals, including Journal of the American Academy of Dermatology, British Journal of Dermatology, International Journal of Dermatology and Lancet, among others.

With close to 150 scientific publications, including over 80 peer-reviewed manuscripts on topics that include recent papers on the effects of curcumin and phosphorylase kinase activity in skin diseases, Dr. Heng's special interest is to attempt to link the pathophysiology and treatment of many dermatologic diseases to their precipitating factors at the basic science level.