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A Personal Critique on the State of Knowledge of Rosacea

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A Medline search of the world literature turned up over 600 papers published in the last ten years in which the term rosacea appeared in the title. National and international dermatologic meetings have prominently featured symposia on acne vulgaris for more than four decades. It is only in the last decade that rosacea has begun to receive comparable attention on the educational programs. Rosacea, an exceedingly distressing, psychologically devastating, life-long disease, for which there is no cure has finally found a place on the radar screen of medicine. Another welcome development which has recently come onto the scene is the creation of the National Rosacea Society in the USA, a publicly funded group, which publishes brief monthly reports dedicated to the needs of rosacea sufferers. Importantly, it also gives research grants to scientists interested in expanding our knowledge of this still mysterious disorder. This encouragement stands in stark contrast to the indifference of the National Institutes of Health, which with an annual budget of nearly 30 billion dollars, has not seen fit to fund a single grant for the investigation of rosacea. I have been turned down twice, based on the grounds, not directly stated of course, that rosacea is merely a “cosmetic” problem more appropriately funded by the skin care industry. As a result, we have voluminous literature, mainly focused on treatments sponsored by commercial interests; perhaps not the most credible source of unbiased research.

My intent in this essay is to take a critical look, admittedly a personal one, on what purports to be our understanding of the diagnosis, treatment, and pathogenesis of rosacea, as described in leading dermatologic texts and in the general literature.

What immediately stands out, which may shock the uninitiated, is the striking degree of controversy, conflict, confusion and contradictions, among the thicket of reports from all over the world. The parvenu to rosacea research will likely be puzzled by these quandaries, which may be off-setting to some, but an attraction to those who like to engage in fields where perplexities reign. There are profound disagreements among “experts” who write and talk about rosacea. I state forthrightly that the state of knowledge regarding the classification, pathogenesis, diagnosis and treatment of rosacea is embarrassing, if not scandalous, when compared to the impressive advances in all other fields of dermatologic research.

The following topics urgently need to be addressed before we can claim that we know as much about rosacea as we do about acne. It is interesting that the original term for rosacea was “acne rosacea”, which has more features in common with acne than currently realized. If the “acne” portion had been retained in the later works, rosacea might have received much greater investigative attention.

Controversies Regarding the Nature, Classification and Diagnosis of Rosacea

This is an embattled area which should make us as red-faced as our patients.

For example, Francis Wilkin of the FDA, whose serious studies have given us impressive insights into the nature and mechanisms of flushing, has proposed some concepts which are inexplicable to most of us. He avers that rosacea is not a disease but a “condition”. He labels rosacea an ideotype, a cluster of signs and symptoms, apparently not a pathologic entity warranting a specific nosologic status. To be sure, rosacea is a multifunctional disorder with many different clinical expressions. Nonetheless, it meets all the classical requirements of a pathologic process, most

obviously the presence of chronic inflammation, both clinically and histologically. Calling rosacea a “condition” downgrades the seriousness of the disorder, perhaps implying that it is only a cosmetic nuisance.

Another distinguished rosacea scholar is Frank Powell whose credentials are impeccable and whose studies are conducted in Ireland. His lectures at international meetings have great educational merit. Yet, he insists that episodes of flushing are not a prerequisite for making a diagnosis of rosacea, and that some patients can develop the full-blown disease without a prior history of frequent flushing. Rebora too, another investigator, says that flushing is not a necessary stage in the sequence leading up to the full-blown “red face” [1]. Some observers think that blushing is more common in the healthy population than in rosacea patients. I disagree with these pronouncements.

I have seen many hundreds of rosacea patients enrolled in our experimental efforts over the past ten years. I have not encountered a single one in whom a history of flushing could not be elicited. This is not a moot point, which cannot be waved away as simply a theoretical argument among quarrelsome scholars. I, and others, regard rosacea as fundamentally a vascular disorder which ineluctably begins with episodes of flushing, eventuating in the “red” face.

I proffer the following observations. Firstly, it is surprisingly difficult in many patients to extract a credible history of flushing. I see patients from far away who have seen multiple physicians but who have never been given a diagnosis of rosacea. Rosacea remains in the shadows, in that sense, a non-disease. The great majority of rosacea sufferers have never seen a physician. The triggers for inducing flushing are idiosyncratic and vary from patient to patient. These include alcoholic beverages, spicy foods, heat, sunlight, exercise, psychological stress, and a variety of other less common triggers. Some patients will react to one or more of these while others are indifferent to the very same stimuli. One has to go through the potential list diligently, one at a time to identify the individual’s specific triggers, a time-consuming enterprise. I have encountered patients who steadfastly deny any form of flushing until I deliberately induce embarrassment by bringing up highly personal matters, or as a last resort, using sexual imagery which then sets off intense flushing. Busy doctors who cannot take a detailed history will frequently miss the diagnosis, complicated further by the fact that rosacea is a great mimic of other unrelated disorders that present with a “red face”. I have often seen classical cases of rosacea mistakenly diagnosed as acne vulgaris, lupus erythematosus, seborrheic dermatitis, contact dermatitis, and other inflammatory diseases. A key point here relates to the difference between blushing and flushing, which is not simply a matter of semantics. Blushing is extremely common in the normal population, often to the same triggers that incite episodes in rosacea patients. I put blushing in a separate category using the following differential points. Though blushing may be intense it usually lasts only a few minutes and is mainly confined to the face. On the other hand flushing, the prototypical hallmark of rosacea, usually lasts for five minutes and more and frequently spreads to the neck and chest, often accompanied by disagreeable sensations and a feeling of heat. When there is ambiguity in separating flushing from blushing it may be helpful to search for other signs. Extra-facial manifestations are common in rosacea but require an examination of the unclothed patient, not very practical in the office setting. One also has to be aware of unusual causes of intense, persistent flushing. Vasodilating drugs, especially niacin, may cause intense, long-lasting, widespread flushing. Wilkin has listed two dozen of these along with disorders like carcinoids which can mimic rosacea clinically [2]. I cite these disputes, not to disparage those who disagree with my views, but rather to emphasize the compelling need to expand support for rosacea research. These and other arguments persist because we have no laboratory tests that will unequivocally establish the diagnosis of rosacea. Moreover, we have no clinical markers that make the diagnosis indisputable. We depend on combining a variety of signs and symptoms to support the diagnosis.

I find it illuminating, even risible that of more than 90 papers which I have reviewed aimed at determining the efficacy of a variety of topical agents, not one concluded that the drug was ineffective. It seems that rosacea is a physician-friendly

disorder in which everything works. This brings to mind the old clinical adage that when everything works, nothing works! Of course, we all understand how it happens that industry supported research is unlikely to yield negative results. The choices that doctors make among many competing drugs are largely empirical and arbitrary, that is to say, they do not meet the requirement of evidence-based medicine. This uncomfortable situation furnishes still another reason for raising up funds to settle these issues by the only known pathway, objective, quantifiable research. I soften these remarks by stating that some industry sponsored research is meritorious, especially from large international skin care companies who have in their employ a cadre of scientists who know the rules of proof.

Nonetheless, therapeutic pessimism is not completely justified since there is a bevy of oral and topical drugs which, in appropriate combinations, make rosacea a treatable disease. This brings to the fore another paradox, namely that we can moderate this disease reasonably well, and greatly improve the quality of life for rosacea sufferers without a substantive understanding of its nature and pathogenesis. We would prefer the reverse situation, in which basic research leads to rational therapies targeted against established etiologic factors. The possibility of understanding rosacea at the molecular level is not a wild or even far off dream, considering the great advances which are so much in evidence in investigatory journals of dermatology. The tools already exist and need only to be placed in the hands of ready and competent scientists.

To these quandaries we can add another disturbing fact, that we cannot fully explain how some of our most effective drugs actually exert their therapeutic benefits. For example, the high efficacy of oral antibiotics, especially tetracyclines, is beyond doubt, a welcome mainstay of treatment. Yet, no pathogenic organism has been identified as causative. Rosacea is not an infectious disease and there is no evidence that antibiotics work by reducing the native microflora, which do not differ from normals. We have to contrive other explanations; the most popular one at present is that tetracyclines possess anti-inflammatory effects, along with other theoretical actions that might affect the course of this complex disease [3]. Tetracyclines have also been shown to have immuno-modulatory effects, to interfere with the production of pro-inflammatory cytokines and even to have unexpected therapeutic benefits in a surprising variety of unrelated dermatologic disorders [4]. We face the same dilemma in regard to the popular metronidazole topicals, which are undoubtedly helpful in maintaining improvement after the disorder has been brought under control. We have no idea how topical metronidazole works or for that matter oral metronidazole which may rival tetracyclines in efficacy [5, 6].

Epidemiological Problems

It is currently taught that rosacea is a common disease but how common is it in quantitative terms? The figures we have to go on are extremely divergent. In a study of Swedish office workers, sitting all day before visual display units, Berg reported a rosacea prevalence of 10%, which qualifies as very common, second only to acne among dermatology diseases [7]. Other investigators in different places report prevalence rates of less than 1%, some as low as 0.1%, qualifying as uncommon. Leading textbooks cautiously submit figures ranging between 2 and 5%, without a shred of evidence to support such figures. The fact is we simply have no idea of the true prevalence since there never has been a credible epidemiological study of a random population. Rosacea specialists whose fame may act as a magnet to attract rosacea patients hundreds, even thousands of miles away, understandably report higher figures. I myself believe that the prevalence may approach 35% in adult women of Scotch-Irish-Welsh Celtic ancestry who are working professionals, competing with aggressive males while trying to raise a family. This is an unprecedented, stressful situation in prosperous countries where women make up more than 50% of the workforce. My estimate of prevalence is of course completely unsubstantiated, a guesstimate as good as or worse than other worthless figures. Rosacea has devastating effects on the quality of life for women. There is far too little appreciation of

the high frequency of depression, anxiety and suicidal thoughts among women sufferers whose well being depends much more than men on an attractive appearance.

This is all very interesting since all the clinical manifestations of rosacea are more severe in men in whom the unchecked disease ends up in rhinophyma, which never occurs in women. There is also a consensus that rosacea is more common in women; though we have no valid data on the actual female to male ratio this might be as high as 3 to 1 if not higher. I recently came to the realization that the photos in major textbooks are nearly always men, giving a vivid but distorted picture of the more usual but less dramatic expressions of the disease in women.

Longitudinal epidemiological studies will bring light into this and related problems but are extremely costly and difficult to carry out, for which no funding is in sight. Some authorities postulate that rosacea may abate or clear spontaneously over time. I have never witnessed such a happening although clinical expressions may fade somewhat over time. Still another controversy surrounds the question of the frequency of premenstrual flares, commonly called "breakouts" in the American idiom. Most patients cite the common occurrence of premenstrual flares but hard evidence is lacking and some authorities deny it altogether. I will soon publish evidence that the response to vasodilating and irritant stimuli generally increases just prior to menstruation, for unknown reasons. Answering that question would cast a lot of light on a litany of other troublesome pre-menstrual complaints.

Unsolved questions plague all aspects of the rosacea scenario. Every experienced rosacea specialist believes that the people most likely to develop rosacea are those where parents or siblings have rosacea. Rosacea is a heritable disease but we have no studies which indicate the mode of transmission. In our laboratory we have developed sophisticated methods for identifying these high-risk patients, often at ages 10 to 15, whom we designate as "pre-rosacea", a term first used by Wilkin. Early diagnosis of the sub-clinical stage allows prevention strategies to halt progression.

Controversies on the Classification of Rosacea

The National Rosacea Society has gathered a panel of experts who have proposed a new classification which has the highly desirable goal of establishing universal standards for classifying the varied expressions of rosacea [8]. This could result in a common terminology which might reduce some of the disputes high-lighted in this essay. Perhaps the reasons why researchers come to opposite conclusions is because they are not dealing with the same categories or stages of this unusually polymorphic disease. Four main types are proposed: the erythemato-telangiectatic type, the papulo-pustular type, ocular rosacea and phymomatous rosacea, of which rhinophyma is the prototype. In my view this is a vast oversimplification which will not solve the diagnostic dilemmas that confront us. I see no reason not to give equal nosologic status to granulomatous rosacea, rosacea conglobata, rosacea inversa (formerly called pyoderma faciale), rosacea fulminans, edematous rosacea (a devastating variety) or combinations with seborrheic dermatitis, lupus erythematosus, acne vulgaris, and still other variants. Reducing the classification to four sub-types does little to clarify and eliminate the inherent complexities of this mysterious disease. Nevertheless, the new classification is a good beginning since it awakens awareness of the necessity to develop robust diagnostic criteria. This is an area where clinicians and basic researchers can profitably come together to provide internationally approved guidelines.

The Papulo-Pustular Imbroglia

Textbook accounts uniformly say that rosacea evolves in distinct stages, starting with episodic flushing, progressing to persistent erythema accompanied by telangiectasias, inevitably followed by a papulo-pustular stage, finally ending in phymomas (rhinophyma). This scheme has some educational value because it depicts the dynamic changes that can occur as this chronic disease progresses through stages of increasing severity, necessitating increasingly more aggressive treatment.

Unfortunately, this scheme is an oversimplification and does not hold up under closer scrutiny; the exceptions are too numerous. The notion that the erythematotelangiectatic stage generally transforms into the papulo-pustular, inflammatory stage is simply wrong and grossly misleading. Firstly, the papulo-pustular stage mainly occurs in males in whom rosacea is a more serious disease at all stages. The papulo-pustular stage is actually uncommon in females. In our experimental studies we utilize mainly women because they are both more compliant and more accessible for repeated observations. We estimate the prevalence of papulo-pustular lesions in female rosacea patients to be no more than 10%. Perhaps geographic location may alter the figures as is the case in Ireland where the population is generally comprised of phototype I Celts, who are also famous for their worship of Bacchus. Australia is also a special case where the population is not only dominantly Celtic but where intensive year-long solar radiation greatly aggravates the clinical manifestations of rosacea, I regard rosacea as belonging to the general class of photosensitivity disorders. Rosacea is less common or at least less severe in darker-skinned phototype IV individuals who do not burn easily and who tan readily. Rosacea is rare in photo-protected, heavily melanized Blacks. The histopathology of rosacea always shows the classic signs of damage to the dermal matrix, namely elastosis, collagenolysis and increased glycosaminoglycans. Separating real rosacea from advanced photodamage in older Celtic men who apparently never had a preceding history of rosacea, is difficult and may be fruitless because the two may come together. As usual, ignorance reigns.

The point here is that the observations made by investigators living in different regions, may be strongly dependent on demographics and geography. For Philadelphia, latitude 42°, we have an associate laboratory in South Philadelphia where the population is dominantly phototype III and IV Italians. Papulo-pustular rosacea is so uncommon there in both men and women that we have great difficulty recruiting a panel of five subjects, despite monetary inducements.

With that background, I advert to another vexing and troublesome problem relating to therapeutic trials. Among more than 60 published reports aimed at demonstrating efficacy, the subjects who participated uniformly had papulo-pustular rosacea. These trials take place under the blurring of being double blind studies, thereby negating skepticism. These studies usually compare the active drug against vehicle or in a comparison between two actives. The universal preference for selecting papulo-pustular patients, completely neglecting the more common erythematotelangiectatic type, is quite easily explained, viz., papulo-pustules can be counted, providing a quantitative basis for estimating efficacy. Numbers are critical for establishing statistical significance, making regulators comfortable in deciding to grant or deny official approval. Statisticians figure prominently in these reports and use a variety of sophisticated methods to substantiate claims of efficacy, even adding mathematically daunting appendices to the test to leave no doubt in the mind of the reader, who like myself, remains uncomprehending. This politically correct numbers game is not a deliberate fraud nor a demonstration that statisticians can be bought off to get the right numbers. Still, statisticians can look at the same data and come to quite different conclusions. Nonetheless, I hold that studies of papulo-pustular rosacea has brought in the marketplace too many drugs of marginal efficacy making it almost impossible for clinicians to make rational choices among the offerings, especially when these are backed up by heavy investments in marketing. I have already mentioned that everything seems to work rather well in papulo-pustular rosacea, so that the "active" agent is predictably superior to the vehicle control. Another sly device is to present the results in terms of percentage reductions in papulo-pustules, not revealing the actual numbers. In that case, we cannot know whether the studies done in different centers are of equivalent merit. Some investigators seem insufficiently aware that papulo-pustules are self-healing lesions, regressing in 3 to 10 days, depending on their depth. Some investigators engage in the self-delusion that papules and pustules can be separately counted, adding to the much vaunted numbers [8]. These are different stages of the same process of follicular inflammation and are often indistinguishable. The fact is that in a 2 to 3 month study, the reductions obtained have nothing to do with

the elimination of existing lesions but simply reflect the ability of the agent to prevent the formation of new ones, which of course is highly desirable.

Accordingly, it is not surprising that nearly every report of controlled trial shows a strong “placebo” response [9]. This too is a misconception since vehicle controls are not placebos in the usual sense of systemic drugs which lack the active ingredient. Vehicles have varying beneficial effects depending on whether they contain constituents which are slightly irritating, a process that in itself recruits inflammatory cells to remove products of tissue breakdown. Components of vehicles that can do this include alcohols, propylene glycol, preservatives like benzalkonium chloride, certain fragrances and others. It is interesting to note the number of reports in which the vehicle control yields results which closely match those of the “active” agent for the first two months reaching statistical significance only after three months. I forbear to identify three references which are numerous enough to take up much space and which are also embarrassing with regard to the quality of rosacea research. For example, I think topical antibiotics like clindamycin alone are nearly worthless. Mills and Kligman fell into this snare when they published decades ago that 2% erythromycin was helpful in rosacea [10]. Combinations of topical antibiotics with other agents, notably benzoyl peroxide, are effective. Since the differences may often be small, statisticians realistically design the study to require large numbers of subjects so as to reach some predetermined goal, for instance to show a superior result for the active agent, say within confidence limits of 95%. Thus statisticians are likely to inform sponsors that large numbers of subjects must be recruited to reach statistical proof, which incidentally is not the same as clinical proof. The usual strategy in this game is to recommend multi-center studies, not uncommonly 6 or more, a formidable attack, to report only mean percentage reductions in papulo-pustules. This conceals what may be serious discrepancies in the results reported from some centers.

I have labored this point to call attention to the snares inherent in trials based on papulo-pustules counts, when in fact we really want to know whether the drug changes the course of the disease regarding meaning of end-points, the frequency of flushing episodes, the intensity of erythema, eradication of telangiectasias, removal of inflammatory histologic infiltrates, improvement of the photodamaged dermal matrix, enhancement of the quality of life and so on. Methodologies already exist using sophisticated methods for visualizing sub-surface changes and modern bioengineering methods to measure accurately these important outcomes, not to mention relief from the psycho-social impediments of this dreadful disorder [11].

Coda

I do not have the heart to take up other hotly contested issues which we will eventually have to deal with, namely the etiologic roles of *Demodex* and *H. pylori*. Controversies rage here also. Our lack of knowledge regarding many aspects regarding the pathogenesis of rosacea has greatly hampered our obligation to provide internationally agreed-upon guidelines for conducting studies which yield concordant results. This will help clinicians select the most effective drugs and aid manufacturers to create superior ones.

I think Napoleon’s remark is appropriate to demonstrate for the public and the authorities what we desperately need to bring rosacea out of the shadows and to add science to clinical empiricism. When asked what was needed to win a war, he is reputed to have said “Three things – money, money and money”.

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