Letters to the Editor

Anti-cook book approach, pro-standardized treatment parameters

Editor – As a plastic and reconstructive surgeon using laser for some considerable time, I could not agree more with the central core idea of Trelles's paper (pp. 237–241), that knowledge of laser-tissue or light-tissue interaction should be used to select ideal treatment parameters on a patient-by-patient basis and that a simplistic 'cook book' approach should be rejected. This of course applies to the treatment of other cutaneous anomalies as much as it does to rejuvenation of photoaged skin – perhaps even more so since, for example, we can often find differences in distribution, density and depth of blood vessels even within the same port wine stain. In such a case, the 'cook book' approach would often leave a patient with an 'after' which is actually worse than the 'before', if the same treatment parameters were applied uniformly over a non-homogeneous lesion.

In previously published works by Trelles *et al.*[1,2] specifically on the use of the combined Er:YAG and CO_2 system for laser resurfacing, it is clear that the parameters he and his colleagues have evolved are based on the photobiological principles that govern the different tissue reactions to the Er:YAG and CO_2 laser wavelengths, whereby the optimal characteristics of wavelengths are applied. The fact that he then asks us to use a narrow range of parameters is not the same as suggesting another blanket 'cook book' approach but should rather be recognized as a valuable step towards standardized treatment parameters (and thus towards reducing the confusion engendered by the vast range of skin resurfacing parameters published elsewhere). In other words, the '*cook book*' approach involves the indiscriminate adoption of one set of parameters, despite differences in lesion size, density and location and indeed the skin type of the patient. Working with a set of *standardized parameters*, on the other hand, allows the clinician to individually tailor the treatment to the particular patient and their lesion but nevertheless to work within a comparatively narrow range of parameters (which have evolved based on the light/tissue interaction associated with the laser or lasers being used, the lesion being treated and the patient's skin type). Although this approach is particularly relevant for cutaneous lesions, it is equally applicable to skin resurfacing or rejuvenation.

Working in Japan, I would like to emphasize, however, the essential difference between Caucasian and Asian skin, which of course includes the Japanese.[3] The former is well recognized as being very robust and resilient to laser-induced secondary hyperpigmentation, so that a comparatively aggressive approach can be applied in many patients. Japanese skin, on the other hand, while recognized as being remarkably tolerant to solar UV exposure, is paradoxically weaker to other exogenous insults, including laser treatment. Severe and long-lasting secondary hyperpigmentation may easily occur in Asians after laser treatment, if parameters suitable for Caucasians are used.

I should like to ask Dr Trelles (and indeed any other readers) what parameters are recommended for this combined laser system in Japanese and other Asian patients, with particular regard to avoiding secondary hyperpigmentation.

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Laser resurfacing today – not all photoscience is photothermal

Editor – There is no doubt that the area of skin rejuvenation is a complex one, with many different laser types and intense pulsed light sources in the arena, and joined very recently by non-invasive light-emitting diode based sources for the non-ablative approach. Deciding on the appropriate parameters for ablative resurfacing or non-ablative skin rejuvenation is just as complex.

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Dr Trelles (pp. 237–241) concentrates on ablative resurfacing and advocates the use of a combined wavelength system with a narrow range of parameters, which has worked extremely well in over 600 patients. His article is of great interest. It contains some extremely important kernel lessons which all practitioners using any form of light to treat any condition must always bear in mind. Unfortunately, some do not.

I was delighted to see that Dr Trelles made the point that the wavelength of a laser or light source is the most important consideration when thinking about how a laser will interact with the target tissue. Naturally, output power and more importantly the power incident on the target tissue (irradiance or power density) will also affect the end clinical result, as will the dose (radiant flux or energy density), but the primary reactions always depend on the wavelength, particularly the depth to which a given wavelength will penetrate. In Dr Trelles's approach, the best characteristics of the two major resurfacing wavelengths, the Er:YAG and the CO_2, are combined in a dual wavelength system. However, the indication of the CO_2 laser in a non-ablative dermal tissue heating mode through the epidermal window cleanly created by the Er:YAG laser is a good example of how understanding laser–tissue interaction can make the parameters work for you. In the mode described by Trelles, no tissue is ablated from the exposed dermis by the incident CO_2 energy: not the usual reaction associated with the CO_2. Instead the tissue is heated to produce the zone of residual thermal damage (RTD) which has been well-reported as being necessary to ensure good wound healing with remodelling that tightens skin and so treats wrinkles. This is making photoscience work for you.

Not all photoscience is photothermal, however. Since the early 1980s, in addition to the surgical application of the laser, I have been particularly interested in the athermal, non-surgical interaction between light and tissue.[1] In his 1999 paper, Trelles and colleagues first looked at the possibility of using the dual wavelength system;[2] they alluded to the athermal photoreactions beyond the RTD zone, and showed in a rabbit ear chamber experiment that the doses of CO_2 he was using produced better neovascularization in a shorter period of time compared with controls. The beneficial effects of low incident doses of light on vascularization have been well-explored in controlled experiments using animal models. One of the first of such papers appeared in 1984, by Kami and colleagues[3] so that the reader can see this is by no means a new discovery, with a more recent paper by Kubota in 2002,[4] and many in between. The RTD in ablative resurfacing is certainly important: I would propose, however, that even more important is the range of athermal photoreactions which take place in the tissue beyond the RTD zone, and it is these which really make lasers and light sources particularly useful in medicine and surgery. This would also explain the less spectacular results seen in skin resurfacing with the Er:YAG laser used on its own in the ablative mode: firstly the zone of RTD is much less, and secondly, very few photons are left to penetrate beyond this zone and be absorbed by the tissue.

I believe that more understanding of these athermal photobiomodulatory effects is absolutely necessary when using laser or other light sources for resurfacing or rejuvenation. Deliberately choosing appropriate parameters to achieve them will improve the good results already achieved.

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Proliferating prevalence of concepts and controversies in atopic eczema

Editor – In his article 'Atopic eczema; what has caused the epidemic in industrialized countries and can early intervention modify the natural history of atopic eczema?' (pp. 202–210) Kristian Thestrup-Pedersen takes us by the hand and shows us around his wonderful collection of atopic eczema observations. We are already familiar with the sometimes distinctive angle that he has developed in his investigations of this disease.[1] While trying to unravel the origin of the increased prevalence of atopic eczema, he touches upon widely varying hypotheses ranging from the increased number of doctors hypothesis, to the 'old mother syndrome' hypothesis. Suggestions as to what to do about it vary from the introduction of probiotics, to the possibly favourable effect of the new topical immunosuppressants on the 'march of atopy', a concept which is presently being investigated. Major and unresolved controversies can be delineated from this discourse.

The primary abnormality of the immune system hypothesis

Many investigators assume atopy is a primary abnormality of the immune system, which leads to the preferential development of type 2 T cell responses towards environmental allergens in the central immune organs. The outcome of this immune aberration is the dissemination of allergen-specific IgE throughout the body. The presence of allergen-specific IgE has been used to confirm the increase in the prevalence of atopy that has occurred over the past 20 years, an increase that is apparent from serial epidemiological studies.[2]

Defining atopy is important for daily practice, as having atopy implies a lifestyle. If one does not accept that allergen-specific IgE is the central core of the syndrome, how does one then

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explain to the patient what he or she has and what to do about allergen avoidance? It has been suggested that patients who have a dermatitis resembling atopic eczema but who have no allergen-specific IgE should be given a diagnosis of atopiform dermatitis[3] and that information about allergen-specific IgE should not be part of their management.

The primary abnormality of epithelial linings hypothesis

However, the opposing view is that atopy is a primary abnormality of the epithelial linings, including keratinocytes, in which there exists a deficiency of protease inhibitors (such that epicutaneous proteases, e.g. from house dust mites and perhaps from *Staphylococcus aureus*, are therefore not inhibited) leading to destruction of the epidermal barrier. These proteases then penetrate the skin and become allergens, which induce allergen-specific immune responses in the central immune organs, including the production of IgE.

By recognizing that allergen avoidance and diets have little effect on the prevention of atopic eczema, Thestrup-Pedersen seems to support the concept that the origin of atopy is to be found within the immune system and not within the keratinocytes.

One would expect that these two opposing views of atopy (a primary abnormality either of the immune system or of epithelial cells), would be translated into the terms intrinsic and extrinsic, respectively. However, confusion is further compounded because the term intrinsic is used for atopic disease in which the immune abnormality, production of allergen-specific IgE, is not detectable, whereas the term extrinsic is used where there is (intrinsic) production of allergen-specific IgE.

The hygiene hypothesis

Another controversy that forms a central theme in this debate is that of the 'hygiene hypothesis'. Essentially, this assumes that we are all born with an immune system that is type 2 T cell skewed. If there are not enough type 1 stimulating signals in early life, such as in the industrialized world with a minimized prevalence of infectious diseases, type 2 skewing persists and ultimately results in IgE production and atopy. The problem with the hygiene hypothesis is that it may be easily falsified, and is thus perhaps scientifically invalid. For example, whilst the prevalence of one type 2 disease, atopy, has been increasing, other type 1 diseases, such as diabetes mellitus and inflammatory bowel disease, have also been increasing. Also, there is no inverse relationship between atopy and type 1 T-cell mediated autoimmune diseases.

A new hypothesis explaining the increased prevalence of atopy is clearly needed.

Comment

Kristian Thestrup-Pedersen brings up many other controversies in atopy, some of them thought-provoking. His contribution also bears witness to the deep lack of mutual understanding and consensus in our different perspectives of this common disease. This inevitably translates itself into uncertainty in the minds of our patients and the general public. Our lack of mutual understanding seems to be used against us and against our patients by the bureaucrats who decide upon the resources they make available for the care of atopic eczema patients. More science and more testable hypotheses are needed to further our understanding of atopy, including atopic eczema. Consensus can hinder that development if it reflects what the majority believe rather than the factual evidence that exists.

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On atopic eczema hypotheses

Editor – In response to my review on atopic eczema (pp. 202–210), Professor Jan Bos (pp. 243–244) reflects on the 'widely varying hypotheses' and 'the deep lack of mutual understanding and consensus in our different perspectives of this common disease'. He states that 'The outcome of this immune aberration is the dissemination of allergen-specific IgE throughout the body' and that 'If one does not accept that allergen-specific IgE is the central core of the syndrome, how does one then explain to the patient what he or she has and what to do about allergen avoidance?' My article is an overview, an armchair look at atopic eczema. Atopic dermatitis is a common skin disease and not knowing its cause leaves room for reflections. The criticism of Jan Bos is, I think, that I throw a lot of pieces up in the air at once saying: here may be the solution to the puzzle. Only having limited space, I aimed to provoke the reader and so I am honoured that Jan Bos is responding.

Two very important issues are raised by Jan Bos.

- Is IgE the central key around which the skin inflammation develops?
- Is 'atopic dermatitis' an immune deviation or is it a keratinocyte disorder?

My simple personal view is that atopic dermatitis truly is an epidermal or keratinocyte disease, although the exact defect(s) is unknown. This then leads to great deviations in the early establishment of the peripheral immune system. We know that the lipid composition of the skin in adults with atopic eczema is changed. We have no studies from infants developing the disorder (for obvious ethical reasons) but it is important, somehow, to obtain data on this.

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Epidermal tissue forms the epithelium of the thymus. In mice, numerous studies document the importance of the thymic epithelium for T lymphocyte maturation. Secondly, studies in mice and man clearly show that IgE switching is determined by T cells. Thus, if there is an abnormal balance in the T cell system, then increased IgE antibodies may develop. This is important. IgE is not a 'primary' outcome of immune reactions towards environmental allergens, it is a result of disturbances of T cells. Many interventional studies have shown the lack of efficacy of diets, allergen avoidance, etc. – except for probiotics (although this needs further documentation). But, to be honest, no interventional study has clearly shown that atopic eczema can be avoided. We have to agree on this.

Jan Bos concludes that my review is 'thought-provoking'. This was my intention. Let us not only read papers showing how TARC, CTACK or cytokine XYZ are highly up-regulated in atopic skin but let us also discuss our different opinions, because these, I hope, can help us better confront a very common disease.

Kristian Thestrup-Pedersen
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The atopic epidemic and the humidity hypothesis

Editor – In his Editorial[1] Chris Rowland Payne brings in another hypothesis that might explain the increasing prevalence of atopic diseases, a trend that hardly anyone denies. In the 'humidity hypothesis', the increase in atopic dermatitis is correlated with the decrease in environmental humidity, especially indoors. Decreased humidity evidently leads to increased skin dryness, itch and thus atopic dermatitis, in patients that are genetically predisposed to that sequence of events.

This is again a hypothesis that puts the weight on the outside world. That is understandable as the genetic predisposition to atopy in the population cannot double in 20 years. Outside factors that are related to the genotype-phenotype switch are likely to be responsible.

The actual number of studies that have been performed to support or falsify this humidity hypothesis is low. In a Japanese study, there was a correlation between severity of atopic dermatitis symptoms and relative lack of indoor humidity.[2] In a Nigerian study, one-third of atopic dermatitis patients reported worsening of their symptoms during the hot humid period,[3] which seems to contradict the humidity hypothesis but heat and air conditioning may have been confounding factors. Another study, this time in the UK, which also seems to falsify the humidity hypothesis, showed a positive correlation between atopic eczema symptoms and dampness of the home.[4] However, this might be related to increased environmental presence of house dust mite allergens.

To further establish the validity of the 'humidity hypothesis', it would be well possible to design additional studies, comparing the incidence and prevalence of atopic diseases in cohorts that differ in environmental humidity, with a sharp eye for confounding factors.

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The humidity hypothesis and atopy

Editor – In his Editorial, Dr Christopher Rowland Payne[1] proposes '*the humidity hypothesis*' as a significant contributor to atopic eczema. I believe that he is correct, as such a hypothesis encompasses the known defects that exist in the atopic skin barrier and the known reductions in skin lipids that exist in atopic skin and which are exacerbated by daily washing.

Still, there are other contributory factors, such as the impaired innate immunity of atopic skin, the immunological changes which skew the peripheral immune system and the increased risk of developing IgE-mediated allergies.

It is amazing that despite the major research efforts into atopic diseases little is yet known of their pathogenesis. But we do know that it is important to use emollients to diminish the risk of flare-ups and additional anti-inflammatory therapy including topical corticosteroids known also to impair the skin barrier through their atrophogenic effect on skin. The introduction of the calcineurin-inhibitors, pimecrolimus and tacrolimus, opens a fully new treatment option, whereby long-term control can be achieved in most children without the risk of adverse effects of corticosteroids.

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The inflammatory hypothesis of ageing: fascinating concept or confusing dogma?

Editor – Dr Perricone claims that inflammation is at the basis of ageing.[1]

We do not share his belief for several reasons. First, the literature he presents to support the concept is a sketchy survey of a limited area of ageing research and leaves untapped a vast array of current knowledge.[2–8] Second, the definitions of key words, including ageing and inflammation, are not given. There remains therefore a possibility of confusion between oxidative stress, stress-induced premature senescence[3] and inflammation, as well as between the different events that influence ageing[2] and the different origins of wrinkles.[9] Third, there is ample evidence that systemic or chronic cutaneous inflammation (e.g. atopic disease, autoimmune disease, etc.) do not particularly worsen ageing. Conversely, steroids and non-steroidal anti-inflammatory drugs and other immune down-regulators[10] do not protect against ageing.

In our view, linking ageing to inflammation is an oversimplification that does not withstand in-depth examination. Rather than raise the standard of scientific progress, this dogma risks reducing the multifaceted ageing process to a cliché. In the ultimate analysis, the proposed unique link between inflammation and ageing is probably not authentic and probably will not stand the test of time.

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