

Letters to the Editor

Allergic contact dermatitis: is the reactive chemistry of skin sensitizers the whole story?

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To the Editor,

A central tenet of the causation of allergic contact dermatitis by skin-sensitizing chemicals is that they must react with skin protein. A brief perusal of any standard textbook on allergic contact dermatitis, or of dermatology journals that contain articles on allergic contact dermatitis, quickly shows the truth that very many skin sensitizers show obvious reactive chemistry (e.g. 1, 2). Such an observation substantiates and reinforces the view that reactive chemistry is essential for skin sensitization. But is this always the case? A careful examination of the same literature also shows that there are a range of substances that appear to cause skin sensitization in humans, but that do not have obvious reactive chemistry associated with them. For some of these, it can be hard to understand how they may be converted, either by oxidation or by metabolism, into reactive species. It is not our intention to suggest that 80 years of our understanding of the key role of reactive chemistry in the induction of skin sensitization and elicitation of allergic contact dermatitis is incorrect, or has been wasted. Overwhelming evidence testifies that this is obviously not the case. However, in seeking to insist that *all* allergic contact dermatitis is dependent on reactive chemistry, it may be that we are sometimes in danger of force fitting the facts to accommodate the dogma, ignoring those instances that point to the existence of complementary mechanisms. Examples include fatty acids, for example the sebacate family (e.g. 3), fatty acid esters such as isopropyl myristate (e.g. 4), benzethonium, and benzalkonium chloride (e.g. 5), the parabens family (6), and materials such as sorbitan sesquioleate (7). This list could easily be made very much longer. Might it not just occasionally be possible that there are alternative mechanisms of specific protein modification by chemicals that do not require reactive chemistry, and where, even if these are not understood at the mechanistic level, an alternative explanation that does

not involve reactive chemistry is actually the correct one? Needless to say, we have little or no knowledge or evidence of what those other mechanisms might be, but clearly they must still possess the elements of induction, elicitation, and chemical specificity. The clinical evidence would also suggest that they are commonly associated with substances that appear to be at most weakly sensitizing.

A separate, but not unrelated, issue is the relationship between the protein reactivity of chemical allergens and relative skin-sensitizing potency. Perhaps because there has been the view that inherent or acquired electrophilicity is a universal mandatory requirement for the successful acquisition of skin sensitization, it has been proposed that this property will therefore provide a sound correlate of sensitizing potency (8). At face value, this might not appear to be unreasonable. The formation of stable associations with protein is, at least in most instances, a requirement for the initiation of a cutaneous immune response and skin sensitization, so why should this parameter not also reflect relative potency? There are two important considerations here. The first is that, even if it is accepted that protein reactivity is indeed the parameter that determines relative skin-sensitizing potency, it is legitimate to question what aspect of the property would be the most relevant. For instance, it has been argued that the kinetics of peptide or protein reactivity will correlate best with potency, but why should this be the case? Why should the speed of conjugate formation with proteins be influential in driving the magnitude of immune priming and the ease with which sensitization is acquired? There are a number of other variables that could also be considered to be relevant. Among these are: the nature and location of the proteins with which a chemical associates, the number of different proteins that are haptenated, and the molar substitution ratio of conjugated proteins. It is entirely possible that these factors may also impact on the induction of immune responses, so there is no reason to suppose that kinetics is the only, or even the most important, metric.

The second issue is that, simply because a factor, or an event or process, is considered to be essential for the acquisition of skin sensitization, it does not necessarily follow that it is related to potency. For a particular

biomarker to be relevant for assessment of relative potency, it has to be both causally and quantitatively associated with the end-point of interest. This may be illustrated best by analogy. There was, some years ago, a requirement in the United Kingdom that, for eligibility to join the police force, applicants had to be of a certain minimum height. Most forces in the United Kingdom required that policemen be 5 ft 8 in. (173 cm) or taller. That height was therefore a threshold requirement for joining the police force. However, there was never a view that there existed a direct correlation between the height of a policeman and the effectiveness (potency) with which he performed his duties. The same applies to skin sensitization; there may be many events that are essential for the acquisition of sensitization, but that do not correlate with potency. These, like the previous minimum height requirement for UK policemen, are threshold effects without a direct quantitative relationship with the effectiveness of the process. It is perfectly possible that

the electrophilic properties of chemicals fall into this category. That is, there is a requirement for threshold levels or greater of conjugate formation with protein, but, after that threshold level has been achieved, any further conjugate production is without impact on the effectiveness of skin sensitization.

To conclude, we are convinced that reactive chemistry is a central element necessary for allergic contact dermatitis, although reaction rate itself may not necessarily correlate with potency, or be the sole driver of allergen potency. What we question is whether reactive chemistry is always an absolute requirement.

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