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# Unravelling the genetic basis of contact allergy. Will this lead to a better understanding of inter-individual susceptibility?

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In their stated quest to unravel the genetic basis of contact allergy in order to explain why some individuals easily become sensitised whilst others do not, McSweeney *et al.*<sup>1</sup> are addressing questions that I too have contemplated.

In the world of botanical dermatology, most individuals who come into contact with poison ivy urushiol, a strong sensitiser, will become sensitised. Sensitisation to urushiol occurs following prohaptan activation to a protein-reactive hapten but to this day the chemical identity of the protein-reactive species remains a matter of conjecture.<sup>2</sup> In this example, a deeper understanding of the genetic basis of the contact allergic reaction is unlikely to provide any clinically useful new insights because the clinically observed reaction is an emergent phenomenon associated with a complex adaptive system<sup>3</sup> (i.e. the immune system), the properties and behaviour of which cannot be predicted from a knowledge of the properties and behaviours of its component parts.

However, plants in general are the source of sensitisers covering the full range from weak through moderate to strong. Those who become polysensitised are usually found to be reacting to weak sensitisers (often of botanical origin), although that does not preclude the possibility that they will also react to moderate and/or strong sensitisers. So, why are these patients so susceptible to sensitisation? Polysensitisation is, again, an emergent phenomenon associated with a complex adaptive system (see above).

Empirically, patients undergoing patch testing, although not polysensitised according to the definition provided by Schnuch *et al.*,<sup>4</sup> will often show positive reactions that are deemed to be of no clinical relevance, i.e. they show a reaction under the forcing conditions of a patch test but do not show clinical symptoms related to that particular substance in day-to-day life. But will a deeper understanding of the genetic basis of the contact allergic reaction shed any new light on this matter? In all probability, we all become sub-clinically sensitised to various substances we encounter in our lives. But what are the circumstances that tip the balance and lead to a clinical manifestation of that sensitisation event?

A conclusion we reached in my research group in the 1990s was that susceptibility to sensitisation by weak and moderate contact sensitisers appears to be inversely related to the capacity of the individual patient to resist oxidative stress. To understand this, it has to be appreciated that living organisms including humans can be thought of as resembling "slow-burning engines".<sup>5</sup> The oxidative processes required to burn fuel molecules are carried out in a reducing environment that acts as a "cooling system" – engines have to be cooled to prevent self-destruction. Redox

homeostasis is maintained by the various components of our antioxidant defences. The principal aqueous phase antioxidant is ascorbic acid (vitamin C); the principal lipid phase antioxidant is tocopherol (vitamin E). These are maintained in a reduced state by glutathione, which in turn is maintained in a reduced state by NADPH. And NADPH is maintained in a reduced state through the activity of mitochondrial processes involving nicotinamide nucleotide transhydrogenase, whereby NADH is used to regenerate NADPH for antioxidant defences in competition with ATP production when tissues are oxidatively stressed, i.e. NADPH production is enhanced to the detriment of ATP synthesis under oxidative stress conditions. NADPH is produced mainly by glucose-6-phosphate dehydrogenase in the pentose phosphate pathway; NADH is derived mainly from dietary fuel molecules via glycolysis and the tricarboxylic acid cycle. Thus, both NADH (the primary fuel molecule) and NADPH (the ultimate antioxidant) are derived from dietary fuel molecules [see Schmidt (1996)<sup>6</sup> for a more detailed account of these events]. However, under circumstances that increase oxidative stress, the protective (antioxidant) reducing environment can be overwhelmed. Individually, some of us are closer to the edge than others because of our different background levels of local or systemic oxidative stress and different capacities at the cellular or tissue level to maintain redox homeostasis.

Oxidative stress sufficient to significantly perturb redox homeostasis will lead to the induction of inflammatory processes mediated (in simple terms) by TNF- $\alpha$  and in turn other cytokines.<sup>7,8</sup> The positive patch test reaction we see can thus be described as a local "cytokine storm", which is biochemically not unlike the cytokine storm that has been described as the principal life-threatening pulmonary event associated with COVID-19.<sup>9</sup> It may not be entirely co-incidental that there have been reports in the media<sup>10</sup> that infection with the SARS-CoV-2 virus has seemingly caused expression of contact allergy to hair dye in persons (hairdressers) who had previously tolerated such exposure. Indeed, a local failure to maintain redox homeostasis could well explain the "angry back syndrome" originally described by Mitchell.<sup>11</sup> It would seem that the SARS-CoV-2 virus is interfering with mitochondrial nicotinamide nucleotide transhydrogenase in such a way as to drive NADPH towards the production of the NADH and the ATP that the virus presumably needs for its own replication, whilst blocking NADPH regeneration. This would create oxidative stress and thereby initiate a cytokine storm. Indeed, the common denominator predisposing patients to severe / life-threatening COVID-19 symptoms and to the expression of allergic contact dermatitis reactions in those who react to weak / moderate sensitizers may be a pre-existing oxidative stress condition (caused, for example, by obesity<sup>12</sup> and type 2 diabetes<sup>13</sup>) or a compromised capacity to resist oxidative stress. Such compromise may happen in many different ways including through an insufficient dietary intake of vitamins C and/or E<sup>14</sup> and/or protein (e.g. egg white) rich in the

cysteine (or methionine) that is needed for glutathione synthesis.<sup>15</sup> Because iron is lost (other than through bleeding) mainly via the shedding of dead skin cells, penetrating contact allergens that are capable of forming "Fenton reactive" complexes with that so-called decompartmentalised iron will be capable of generating oxidative stress through redox cycling (see Schmidt *et al.* 1997).<sup>16</sup> Therefore, a diet rich in iron (e.g. red meat) may increase the probability of becoming sensitised to any (weak) allergen that is capable of forming such an iron-prohaptene complex. Not only diet but also medication being taken by the patient could also conceivably contribute to perturbation of redox homeostasis. This would apply especially to those drugs that are excreted as mercapturates (because they deplete glutathione). The most important is probably paracetamol / acetaminophen (see Schmidt 1993).<sup>17</sup>

So, rather than seeking to better understand the genetic basis of contact allergy in order to explain why some individuals easily become sensitised whilst others do not, I would suggest that there is still much to be learned simply from asking patients to talk about how much and what they eat and don't eat, and what medication they are taking. In particular, paracetamol is normally taken (by adults) in 1 gram doses four times a day, a quantity that would be expected to have a significant impact on available glutathione and hence on the ability to maintain redox homeostasis, especially in those individuals who may also have an inadequate dietary intake of vitamin C and vitamin E and/or a high intake of red meat or other sources of iron.

In addition, or instead, a failure of glucose-6-phosphate dehydrogenase [G6PD] to maintain adequate NADPH levels when a tissue / organ is oxidatively stressed has to be seen as a highly probable underlying "lesion", not only in polysensitised allergic contact dermatitis patients but also in COVID patients.<sup>18</sup> G6PD deficiency is well documented as being the most common human enzyme defect and over 140 variants / mutations are known.<sup>19</sup>

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