Reply to Drs Little, Colegrove, Sadd and Schimd-Hempel

Sir,

We welcome the response from Drs Little and colleagues on our article but, first, would like to make clear that, contrary to their claims, we do not take issue with the evolutionary approach to study immunity. Neither do we dismiss its role in contributing to understanding it in whole organisms. This is explicitly stated in our concluding comments. What we do assert is that observations of such phenomena *alone* are insufficient to erect a new model of invertebrate immunology, especially where they sweep aside established facts obtained by an extensive mechanistic research. Our article makes clear that we recognize the value of phenomenological observations of whole organisms as the *starting* point for constructing working hypotheses but they are just the first step and a long way from being a new paradigm. They must be followed by experiments to explore likely mechanisms and to test the robustness of any theory erected. Such steps form the basis of all Popperian researches and their absence is detrimental to the advancement of this field of research.

Too often, the role of immunity in whole organisms is assumed, not demonstrated. No matter how one looks at it, fecundity is not an immune process and is not a direct measure of immune functioning. Invocation of immunity is but one interpretation of several possible alternatives. Indeed, many of the reports of "apparent" specificity and memory in invertebrate immunity made 30 or more years ago (which actually show very small and short-lived responses) have now been explained in the light of more recent work. Apparent adaptive responses may yet turn out to be equally explicable but, in any case, will only be definitively explained in the light of thorough mechanistic study.

What we call for is rigorous testing of all possible hypotheses with some solid evidence of the underlying immune mechanisms which, with the technologies available today, should not represent a significant challenge. The biochemistry of the invertebrate immune system is now well understood, particularly in arthropods. There are powerful techniques with which to probe at the gene, protein and cell levels and rapidly expanding genomic and proteomic datasets. These approaches surely must be embraced if 'radical' new theories and ideas are to be proven as truths and not remain as conjecture.

Perhaps one of the problems is the use of terms and the definitions adopted by different camps. Sometimes the terms 'adaptive' and 'acquired' are used interchangeably, sometimes not, depending on whether antibodies and T lymphocytes are considered key criteria. In evolutionary biology, the term 'adaptive' can have a less-constrained meaning: 'alter to fit better' within the life of the organism, for example. Moreover, innate and acquired responses both exhibit some, albeit different, degrees of phenotypic plasticity. In a few species of invertebrates, the repertoire of receptors can be expanded epigenetically. However, this is not the same as true acquired immunity of gnathostomes and cannot be regarded as an equivalent unless a related expansion of specific effectors and memory are also demonstrated.

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