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## Skin-test responses to mycobacteria in atopy and asthma

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In a recent publication in *Allergy*, Strannegård et al. investigated the correlation between the prevalence of allergy in children, and their skin-test responses to three mycobacterial antigens (1). This topic is of great interest because decreased contact with mycobacteria would fit the "hygiene hypothesis", which can be summarized as the view that modern hygiene is depriving the immune system of Th1-inducing input during early life, and that a consequent lack of regulatory type 1 cytokines is resulting in excessive activity of the Th2 system, and in a lowering of the threshold for allergic responses (2, 3). Some support has come from the report that there is an inverse relationship between atopy and tuberculin positivity in Japanese school-children (4), and from work in experimental models where certain mycobacterial preparations will block induction of Th2 responses (5), or even switch off previously established ones (6). The idea has become still more attractive since the revelation that children with defective receptors for interferon gamma (IFN- $\gamma$ ) or interleukin-12 (IL-12) die of fatal infections caused by environmental mycobacteria (7, 8). This suggests that these organisms may be constantly "exercising" the Th1 systems of those normal children that encounter them.

Strannegård et al. (1) found that the prevalence of allergies was reduced among those immigrant or adopted children who had received BCG vaccine abroad. On the other hand, there was an *increased* incidence of skin-test positivity to *M. scrofulaceum* and *M. avium* in Swedish-born children who had allergies.

To interpret these findings, it is essential to be aware of the quite different significance of skin-test responses to distinct classes of mycobacterial antigen (Fig. 1). Some individuals respond to the "common" mycobacterial antigens, which include such crucial immunoregulatory anti-

**Date:**

Accepted for publication 19 November 1998

**To cite this article:**

Rook G.A.W. & Stanford J.L. Skin-test responses to mycobacteria in atopy and asthma. *Allergy* 1999, **54**, 285–286.

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ISSN 0105-4538

## Two types of skin-test positivity to mycobacterial antigens

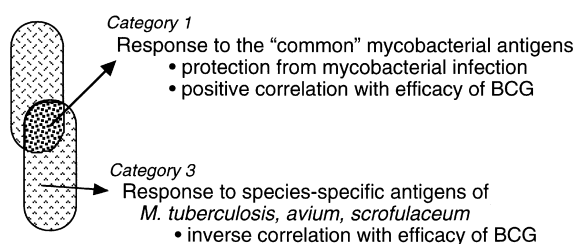


Figure 1. Category 1 skin-test responders recognize “common” mycobacterial antigens, which include proteins, such as heat-shock proteins, with important immunoregulatory roles. This is the protective response, and is likely to be the one that can downregulate the tendency to develop allergies. Category 3 responders recognize species-specific epitopes. Individuals with no positive skin-test responses are regarded as category 2. These categories are defined and justified in references 10–14.

gens as the heat-shock proteins. These antigens are the principal targets for immunity (9), and skin-test responsiveness to them correlates with protection from tuberculosis and leprosy, and with efficacy of BCG vaccination against both infections (10). Other individuals respond to the species-specific components of organisms with which they have been clinically or subclinically infected (10). This type of responsiveness does not always correlate with protection. For instance, skin-test positivity to *M. scrofulaceum* was

inversely correlated with the efficacy of BCG vaccination in Burma (10).

Mathematical models show that these categories of responder represent genuinely distinct populations (11, 12), and this is confirmed by the observation that they correlate with HLA phenotypes (13, 14). These results also suggested that the mechanisms of response, as well as the specificity, are different.

For these reasons, we feel that the data of Strannegård et al. (1) may be open to an alternative interpretation. Skin-test positivity to *M. scrofulaceum* in urban Swedish children is likely to be a consequence of the failure of priming of responses to the protective common antigens by BCG (which was not given) or environmental saprophytes (not encountered). This results in more subclinical infection with *M. scrofulaceum*, and consequent category 3 responsiveness to it (Fig. 1) (15). This type of skin-test positivity would be expected to correlate with allergies, rather than with their absence.

A further prediction of this suggestion is that the skin-test-positive, BCG-vaccinated children from overseas that were also included in the study of Strannegård et al. may have had category 1 responses, while the *M. scrofulaceum*-responsive Swedish-born children may have had category 3 responses. This is relatively easily tested.

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