

Letter to the editor

Skin reactivity to histamine: *Eppur si muove*

In his editorial in the May issue of *Allergy*, S. Dreborg expressed his opinions on theoretical and methodological aspects of the skin reactivity to histamine (1), a key issue in clinical allergy. He also commented on an epidemiologic study by our group (2) reporting a progressive increase in histamine skin reactivity among subsequent cohorts of Italian 9- and 13-year-old schoolchildren examined between 1983 and 1996.

Many points of Dreborg's editorial are of general importance but do not pertain to our study, because they focus on methodological aspects of the skin prick test as a technique to diagnose IgE-mediated skin reactivity to allergens, aspects such as the determination of the relative potency of allergenic extracts and their standardization, the use of allergen skin prick tests in epidemiology, and the use of histamine as a reference for allergen skin prick tests.

Some of his other comments and advice/recommendations are of even greater general importance, such as his points that skin testing should be considered a laboratory method, and that there should be appropriate training of staff to do the testing. No one could disagree with these observations.

However, other comments by him pertain to specific methodological aspects of our study and require our reply. He first questions our use of Pepys' technique in prick testing because it has been out of use for many years. Dreborg, however, himself answers this objection by observing that we started this study in 1983 and so had to continue using the same methodology thereafter to ensure standardization of methods and comparability of data over time.

His second objection is that the coefficient of variation of measures of wheal diameters of histamine 10 mg/ml in our pilot studies before each survey (CV 8–20.5%) should be considered "too low compared with data obtained in most clinics in Europe" (3). This statement is rather surprising: it is true that in the quoted paper Dreborg et al. report that the CV was 15–50%, but this variability was relative to data obtained by calculating wheal areas: as the authors themselves write, this corresponds to a CV of 7–25% when simply dealing with wheal diameters (as we did). However, it is true that we achieved a good inter-observer CV (which was often well below 20%) in pilot studies precisely through "appropriate training of testing personnel". This is exactly what Dreborg claims should be done in epidemiologic studies. Interobserver CV values similar to ours were obtained also by many other researchers (4–7).

Dreborg also comments that we found subjects with a larger wheal to a lower histamine concentration, and that this is a sign of poor standardization. Indeed, we found 10/536 subjects with these characteristics. Most of these were subjects with a null reaction to histamine 1 mg/ml and with a 1–2-mm reaction to histamine 0.2%. We consider this very low rate of inconsistent values (1.8%) to be a proof of good, rather than bad, standardization.

His third objection is that we used a reading time of 10 min, instead of the recommended 15 min. During pilot studies, we found no significant differences between responses to histamine read at 10 or 15 min. Indeed, Østerballe & Weeke (8) demonstrated that the wheal size to histamine peaks earlier (9–12 min) than that to allergens (13–16 min).

His fourth objection is that we have shown (Fig. 3 in Ref. 2) a mean value of wheal reactivity below 1 mm to histamine 0.2 mg/ml. Dreborg comments that a wheal size smaller than a cutoff of 2 mm should not be used in epidemiologic analyses. We agree completely, and that is why we assigned a value of 0 to wheals of <2 mm in diameter when we calculated means. Many subjects had a reaction of this kind to the lowest concentration of histamine (0.2 mg/ml); however, a few others had wheal reactions of 2, 3, or >3 mm. Therefore, the mean value was higher than 0 but below 1. We hope that this explanation clarifies the distinction between individual measures and the mean of individual measures (we showed only the latter).

Furthermore, we wish to stress that our study was not intended to compare our data with those of other studies, an aim that would have required adhesion to international standard procedures. We aimed to standardize procedures within our group to yield good comparability of our data over time. Skin prick test procedures are so complex that we cannot exclude possible imprecisions. Nevertheless, these would have confounded the data, rather than produced the trend observed and were probably too small to justify the steepness of the trend. We base this conclusion also on the evidence that histamine reactivity measured in the same subjects at the age of 9 years in 1983 and later, at the age of 13 in 1987, was only slightly higher (3.25 vs 3.89, histamine 10 mg/ml) (Fig. 3, Ref. 2), an expected difference that reflects the effect of age. Methodological artifacts would have differently affected the results.

Finally, we were rather surprised that the core message of our paper, i.e., the evidence that skin reactivity to histamine may be on the increase in a

Letter to the editor

Western country, was completely overlooked in the editorial. Dreborg comments, "To me, this hypothesis does not sound plausible, since it would indicate either a change in the genetics of Italian children or an increase in the nonspecific reactivity of the skin of most children similar to that in the bronchi of asthmatics." We obviously excluded any genetic implications in our results and considered it extremely plausible that a phenomenon already observed at the bronchial level (increase of the responsiveness to histamine in the population) would involve also the skin.

We understand that reactivity to histamine has been chosen as the reference standard for skin test reactivity to allergens, and also that it was considered to be some "fixed" biologic variable not subject to environmental influence. We believe, however, that nothing remains

"fixed" in biology, any more than in astronomy, and that Galileo's saying, *Eppur si muove*, might be true also of skin reactivity to histamine in populations with a changing lifestyle. We may well be wrong, but the only scientific way to approach our hypothesis is to test it in new epidemiologic studies, rather than to reject it a priori.

*Prof. Roberto Ronchetti
(on behalf of all authors of Ref. 2)
II Cattedra di Clinica Pediatrica
Università di Roma "La Sapienza"
Viale Regina Elena, 324
00161 Rome
Italy*

References

1. DREBORG S. Histamine reactivity of the skin [Editorial]. *Allergy* 2001;**56**:359–364.
2. RONCHETTI R, PIA VILLA MP, CIOFETTA G, BARRETO M, FALASCA C, MARTELLA S. Changes over 13 years in skin reactivity to histamine in cohorts of children aged 9–13 years. *Allergy* 2001;**56**:436–441.
3. DREBORG S, BASOMBA A, BELIN L, et al. Biological equilibration of allergen preparation: methodological aspects and reproducibility. *Clin Allergy* 1987;**17**:537–550.
4. SKASSA-BRODIEK W, MANDERSCHIED JC, MICHEL FB, BOUSQUET J. Skin test reactivity to histamine from infancy to old age. *J Allergy Clin Immunol* 1987;**80**:711–716.
5. DEMOLY P, BOUSQUET J, MANDERSCHIED JC, DREBORG S, DHIVERT H, MICHEL FB. Precision of skin prick and puncture tests with nine methods. *J Allergy Clin Immunol* 1991;**88**:758–762.
6. NELSON HS, LAHR J, BUCHMEIER A, MCCORMICK D. Evaluation of devices for skin prick testing. *J Allergy Clin Immunol* 1998;**101**(2 Pt 1):153–156.
7. NIEMEIJER NR, GOEDEWAAGEN B, KAUFFMAN HF, DE MONCHY JGR. Optimization of skin testing. I. Choosing allergen concentrations and cutoff values by factorial design. *Allergy* 1993;**48**:491–497.
8. ØSTERBALLE O, WEEKE B. A new lancet for skin prick testing. *Allergy* 1979;**34**:209–212.