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Autologous plasma and serum skin test in chronic urticaria

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MADAM, We were surprised to read the study by Yildiz et al.¹ about the use of autologous plasma skin test (APST) in

patients with chronic urticaria (CU), and would like to comment on some aspects of this issue.

Yildiz et al.¹ claim that seven of 42 patients with CU and four of 35 healthy subjects were positive on intradermal testing with sodium citrate diluted with saline solution, and conclude that APST was never positive if evaluated with negative controls. However, their conclusion is undermined by the lack of definition of positivity of intradermal testing with sodium citrate. In our experience, we have not observed any skin reaction to intradermal injection with sodium citrate diluted with saline solution unless the subject shows a marked dermatographism and reacts to saline solution too. If sodium citrate were able to induce nonspecific weal-and-flare reactions as claimed by Yildiz et al., one would expect to find a large prevalence of normal subjects scoring positive on APST but, again, this has never been observed in our series^{2–4} as well as by other authors.⁵ In the original paper published in the *Journal of Allergy and Clinical Immunology*,² to assess the specificity of skin reactions induced by autologous plasma, 10 patients [five positive on autologous serum skin test (ASST) and eight on APST] underwent further intradermal tests using sodium citrate 0.125 mol L⁻¹ in saline; no patient reacted to this solution. In particular, three of the 10 patients tested were APST positive and both ASST and sodium citrate negative. Moreover, no skin reactivity to APST was observed in 10 subjects with allergic rhinitis, or in five subjects with contact dermatitis.

Another surprising aspect of the paper by Yildiz et al.¹ is the assumption that APST was positive 'if a plasma-induced weal-and-flare had a diameter > 3 mm and the ASST, S [saline] and SC [sodium citrate] tests were negative'. In our view this way of grading the results is questionable. As plasma (like serum) contains autoantibodies to IgE and/or to high-affinity IgE receptor (FcεRI), both tests are expected to score positive in patients with autoimmune CU. In effect, in our first study of APST,² we clearly reported that APST scored positive in virtually all ASST-positive patients with CU. However, we also found a proportion of ASST-negative patients who scored positive on APST which prompted us to hypothesize a role played by coagulation factors in the skin reaction and led us to perform all the subsequent investigations on the coagulation cascade.^{6–8} We are well aware that the proportion of APST-positive/ASST-negative patients with CU may change on the basis of the population studied, patient selection, skill in performing and reading the intradermal tests, disease activity, criteria adopted for scoring the test (for example, we believe that a marked flare without a weal should be considered positive) etc., but we hardly ever see APST-negative/ASST-positive patients with CU, an observation that has been confirmed also by other authors.^{9–11}

Finally, the surprisingly high percentage of ASST positivity in healthy subjects (more than 30%) elicits several perplexities about the way Yildiz et al.¹ interpret the skin reactivity to autologous serum. In fact, the general experience, including that of the expert panel of the European Academy of Allergology and Clinical Immunology that has prepared a consensus document on ASST in CU, is that healthy controls do not have

positive ASST responses.¹² We believe that skin reactivity to intradermal testing with serum as well as sodium citrate can be overestimated if it is not adequately compared with the skin reaction elicited by saline injection and dermatographism is not taken into account.

In conclusion, although we agree that APST has not been superior to ASST in most studies carried out in centres other than ours (although APST scored more frequently positive than ASST in several cases^{9,11}) it has to be clearly stated that both ASST and APST are specific tests that may score positive only in CU and a few other clinical conditions.

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Autologous plasma and serum skin test in chronic urticaria: reply from authors

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MADAM, First of all, we thank Asero et al.¹ for their valuable contributions. We believe that our study is different from previous ones in that it used modified criteria for evaluating the autologous plasma skin test (APST). We added both sodium citrate in saline (SC) and an autologous serum skin test (ASST) as additional items.² In our study, APST was interpreted as positive if a plasma-induced weal-and-flare had a diameter > 3 mm and the ASST, S (saline) and SC tests were negative.² In the previous studies, only an unequivocal weal-and-flare reaction with a weal diameter of at least 3 mm in the absence of any reaction to saline was considered as a positive response.^{3,4}

It is well known (as Asero et al. also mentioned in their letter) that both plasma and serum (used in APST and ASST) contain autoantibodies (developed against FcεRI and IgE) and histamine-releasing factors (HRFs). Plasma also contains coagulation factors (especially thrombin) and plasma preparations contain SC. The positive reaction of APST may originate from SC, thrombin, autoantibodies and HRFs. So, SC was included in the test panel as a negative control. We believe that this is a logical practice and will be accepted by the investigators. In the literature, saline has been used as a negative control test for ASST and APST in almost all studies.^{3,4} In addition to saline, we think that SC should be used as a negative control in APST, to differentiate whether the positivity originated from SC or from the plasma itself. From this point of view, we modified the APST evaluation criteria and added SC as a negative control.

We also included ASST into the evaluation criteria of APST to clarify the individual role of 'thrombin' in the pathogenesis of chronic urticaria (CU). In this way, we excluded positive ASST results which depend on autoantibodies and HRFs. We tried to determine the additional value of the APST, and our study results should be evaluated on the basis of this approach.

Modified criteria were used to evaluate the APST in our study.² We added SC and ASST as negative controls.^{2,3} When