



Correspondence

A critical need

Increasing interest in the field of allergy and immunology



We read with interest Dr Scherzer's¹ article on the downward trend in applicants for allergy and immunology (AI) fellowship programs, and we commend Dr Scherzer for exploring approaches to increase interest.

As Dr Scherzer states, there is limited exposure in medical school and residency to the field of AI and a decrease in the number of fellowship candidates per fellowship position. However, AI does seem to offer the work–life balance and clinical experiences that many learners might want in a fellowship. We ask Dr Scherzer whether she has been able to identify any negative perceptions about the field or aspects of the practice of AI that learners find undesirable.

Dr Scherzer suggests encouraging allergists who work outside academic medical centers to allow learners to rotate in their offices. We

ask Dr Scherzer about her views on how medical students and schools with limited resources could encourage physicians in the private sector to be more involved in the education of future AI providers.

If the downward trend were to continue to the point where the available positions outnumbered the candidates, then we ask Dr Scherzer whether this might lead to closure of AI fellowship programs to redistribute Medicare graduate medical education funding.

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Author's reply



I thank Okafor et al for their interest in our article “A Critical Need: Increasing Interest in the Field of Allergy and Immunology in Medical Students and Residents” and their thoughtful questions. The general downward trend in the number of candidates per fellowship position in the Allergy and Immunology (AI) fellowship training program match from 1.7 in 2008 to 1.0 in 2018 is concerning and an area of discussion and planning for many in the field.^{1,2} A study by Macy et al³ revealed that the key time in the decision-making process on whether to pursue fellowship training could be in the final years of medical school or early in primary residency training, so those points in one's career might be the best focus of any interventions to increase engagement and interest in AI.³ As noted in the original manuscript, often those early learners may not have a significant exposure to AI at their home medical centers, because many of them do not have an AI fellowship training program or AI faculty on staff at their institution. That being said, exposure to the

discipline of AI does not only occur through hospital-based practitioners. The field of AI is fortunate to have many board-certified practitioners in private practice settings across the country who are very engaged and provide outstanding education to young learners. This may occur in their private practice office or if the providers also practice at a local hospital clinic, in that setting. At this time, I am unaware of any negative perceptions about the field of AI, but further consideration of that question could be both interesting and helpful as we work to increase the number of residents pursuing AI fellowship training. Although funding for graduate medical education training programs is competitive, the goal would be to ensure that none of the current excellent AI fellowship programs would need to close secondary to a decline in the number of applicants. Many in AI are working within our large national societies and local communities to increase the number of top tier candidates applying to AI fellowship training programs. Hopefully working within the AI community with those who practice in all settings, we can increase interest in our field and the fellowship applicant pool.

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Is hereditary angioedema related to an increased risk of atherosclerosis?



We paid close attention in reading the interesting paper by Nebenführer et al,¹ whose findings excluded the presence of endothelial dysfunction in hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) patients. Their results are opposite of those recently published by our research group.² Because the issue is important, impaired endothelial function being correlated with future occurrences of adverse cardiovascular events and cardiac death,³ we think that a few points should be worthy of debate.

The relationship between hereditary angioedema (HAE) and atherosclerosis is undoubtedly controversial, although some evidence tends to confirm it.^{2,4–6} Furthermore, regarding a possible pathophysiological explanation, HAE may share an endothelial dysfunction that was probably not caused by the disease per se, but instead by bradykinin receptor–asymmetric dimethylarginine (ADMA) pathway activation or danazol, resulting in unfavorable changes in serum lipid levels.^{1,2}

Based on these premises, many factors may have contributed to the varying results:

- The participants' age, as honestly acknowledged by the authors, which was considerably lower than that of the subjects in our study (mean age, approximately 30 vs 48 years). Endothelial function is known to begin to deteriorate at approximately the end of the fourth decade of life, and we found a strong relationship between reactive hyperemia and chronological age as well.^{1,2}
- Gender distribution. In our sample size, 75% of the recruited patients were female, and 48% were female in the study by Nebenführer. Hereditary angioedema is likely to be more frequent and severe in women than in men.⁷
- Again, as pointed out by the authors, the distinct techniques of measurements (fingertip plethysmography vs flow-mediated dilation at the brachial artery) also may have increased discrepancy in the results, because they rely on different physiological processes/responses¹
- We enrolled C1-INH-HAE individuals as well as a subgroup of HAE patients with mutations in the *F12* gene (FXII-HAE), whereas in the study by Nebenführer et al, only C1-INH-HAE patients were recruited. Although we did not find statistically significant differences when comparing reactive hyperemia in C1-INH-HAE and FXII-HAE subgroups, this issue also may explain the reported different findings.^{1,2}

- We also measured blood levels of ADMA, a strong inhibitor of nitric oxide synthesis, whose increase occurs simultaneously with an increase in global cardiovascular risk.⁸ A statistically significant inverse correlation was also found between reactive hyperemia and patients' ADMA levels, even when excluding the possible influence of lipids.¹ The increased ADMA hematic concentration is another strong factor supporting the hypothesis of an accelerated atherosclerotic process in HAE patients.
- Finally, none of our patients was taking danazol or attenuated androgens, so our findings were not influenced by these drugs, which are known to impair lipid levels, thus leading to accelerated atherosclerosis, and also to increased coagulation activation when used in long-term prophylaxis.^{4,9} This striking difference with the other patients gives increasing reliability to our findings.

To sum up, the marked heterogeneity in the 2 studies' designs also may explain their different results. Because HAE is a rare disease, with consequent difficulties in recruiting enough patients to apply multivariate statistical analysis, now is the time to plan a multicentric study, with clear criteria of inclusion/exclusion, to definitively resolve this tricky issue.

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