

## **40-year career centers on translational research**

*By Albert L. Sheffer, MD, FAAAAI*

In the past 40 years, collaboration with **K. Frank Austen, MD, FAAAAI**, and the members of his laboratory has provided me with an outstanding opportunity to participate in translational research. Shortly after beginning my allergy/clinical immunology practice, I encountered a family with hereditary angioedema (HAE). This disorder challenged us to define the disease pathologically, clinically and therapeutically.

Austen's newly developed complement laboratory's diagnostic contributions were based upon a Donaldson and Evans report that C 1 Inhibitor (C1INH) deficiency was associated with HAE enhanced disorder. The first pathologic study of HAE in collaboration with Craig, Willms-Kretschmer, Rosen and Austen indicated that many patients with HAE had undergone needless laparotomy, with tissues demonstrating the non-inflammatory edema involving the submucosa of the small bowel characteristic of HAE.

The development of diagnostic tests with sensitivity suitable to monitor treatment efficacy permitted the development of several therapeutic interventions. Rosen, Alper, Pensky, et al were the first to call attention to the variant form of the disease. They observed that 15% of the families had a non-functional C1INH. Shortly thereafter, Caldwell, Schur, Ruddy and Austen described the acquired form of angioedema, and Geha, Quinti, Austen, Cicardi, Rosen and I defined the presence of an anti-idiotypic antibody in a group of patients with acquired C1INH deficiency.

Spaulding had called attention to the efficacy of methyltestosterone in treating two patients with HAE. We then administered sublingual methyltestosterone to two men and two women with HAE. Both women became pregnant during the study with subsequent normal births, indicating the lack of ovarian suppression on this low dosage with control of the HAE symptoms. Later, we successfully treated 18 patients with the anti-fibrinolytic agent tranexamic acid (trans 4-aminomethylcyclohexane-1-carboxylic acid) at least 10 times more effective as an inhibitor of plasminogen activation than EACA (epsilon amino caproic acid).

Tranexamic acid was withdrawn from the United States market because of serious adverse side-effects in dogs, although it is currently being utilized to treat HAE in Europe. A double-blind trial using oxymetholone, a 17- $\alpha$ -alkylated anabolic agent with impeded androgenic effect was then executed with significant suppression of symptoms in 27 patients. This agent clearly demonstrated that at dosages unassociated with adverse side effects and without increments in the level of the C1INH, HAE symptoms could be reduced, in fact, eliminated.

Subsequently, Stanozolol, an anabolic agent with impeded androgenic effect and with a 30:1 anabolic: androgenic therapeutic ration, became available. We surveyed our patients who had received the drug for a decade. There were few side effects at the low dosages required to maintain a symptom-free state.

We are currently evaluating nearly 50 patients who have taken the drug prophylactically for 25 years, with symptom relief and without significant adverse side effects. Some patients have gained weight, developed slight hirsutism and/or have noted reduced HDL, but few required emergency care for their HAE.

Newer modalities of therapy are being developed for HAE. However, such interventions address mainly acute attacks. These include replacement therapy with the purified C 1 INH protein, as well as the utilization of a kallikrein inhibitor and a bradykinin receptor antagonist. These substances are administered parenterally, whereas stanozolol is an orally administered prophylactic agent, with few side effects at the dosages required to control and prevent attacks. It is available in the United States at local drug stores, compounded by the pharmacist.

Another contribution from this translational research collaboration related to the study of physical allergies. Soter, Wasserman, McFadden and Austen had confirmed earlier reports of histamine release from the effluent vasculature in patients with cold urticaria, when challenged by extremity immersion in an ice-water bath. There was clear evidence of mast cell activation by histologic assessment of induced lesional biopsies.

Austen and I reported 16 patients who experienced exercise-induced anaphylaxis over the preceding decade. Information was available regarding another seven patients by correspondence with referring physicians. That 1980 report summarized the precipitating events, symptoms and signs in the directly assessed patients. In subsequent assessments in collaboration with Soter and McFadden, we demonstrated in seven patients undergoing exercise challenge that histamine levels rose in those patients developing symptoms with the exercise challenge. These studies suggested that exercise-induced anaphylaxis was a unique physical allergy distinct from cholinergic urticaria.

In collaboration with Tong, Murphy, Lewis and McFadden, we demonstrated mast cell activation (degranulation) occurring with the onset of induced symptoms of exercise-related anaphylaxis. Studies relating to the pathogenesis of this disorder have been very provocative. There appears to be a requirement for a companion signal to exercise. Therapy for this disorder includes modifying exercise with avoidance of environmental and ingested precipitants.

Since my early days of training, the effective treatment of asthma, as well as its etiology and the preventions of asthma fatalities, have been of concern for me. I edited a monograph pertaining to fatal asthma, to which many of the world's asthma specialists contributed. My interest in asthma continued in collaboration with **Claude Lenfant, MD, FAAAAI**, then director of the National Heart, Lung and Blood Institute (NHLBI) and Suzanne S. Hurd, PhD, then director of the Lung Division of the NHLBI. Appointed chairman of the first panel of the National Asthma Education and Prevention Program (NAEPP), I was assisted by a panel of asthma specialists and NHLBI administrators. We edited the first Guidelines to the Diagnosis and Management of Asthma. Subsequent revisions by Shirley Murphy, MD, and **William W. Busse, MD, FAAAAI**, have maintained the current relevance of the program.

The Global Initiative of Asthma (GINA), developed by Hurd, extended the relevance of the NAEPP to the international community. Many members of the World Allergy Organization (WAO) are participants in GINA. Romain A. Pauwels, MD, PhD, and I were the early chairmen of GINA. More currently, **Stephen T. Holgate, MD, DSc, FAAAAI**; Jeffrey M. Drazen, MD; Paul M. O'Byrne, MD; and many others have continued their support of GINA, making it an important international guide to asthma diagnosis and therapy.

I have enjoyed the opportunity to assess various clinical entities with basic scientists who provided me with the assistance required to execute such translational research projects. As a consequence, I have collaborated with many outstanding medical scientists.

The most memorable of these interactions were the Brigham and Women's Hospital Allergy Immunology fellows, many who now direct their own laboratories. Currently a clinical professor of medicine at Harvard Medical School, I've been honored by the WAO as the recipient of the Salter Award for Clinical Excellence and by the AAAAI with the Distinguished Service and Distinguished Clinician Awards.