Academics chosen as career choice in allergy/immunology

By Charles E. Reed, MD, FAAAAI

Looking back over 50 years it is difficult for me to decide which one or two contributions were most important. What seemed important at the time has often turned out not so important after all. However, I did choose an academic career for two reasons that are still important: to train more allergists for an underrepresented specialty, and to search for answers to questions about the pathogenesis of allergic diseases in order to improve patient care.

The first fellow finished the allergy training program at the University of Wisconsin in 1962, and since then more than 60 physicians have trained under my direction at Wisconsin or Mayo. This is the contribution that gives me the most satisfaction. Several former fellows now direct research and training programs themselves, so my original goal of increasing the number of practicing allergists has been achieved.

Medical specialty training programs are like a family, and like a family they have a lineage. Ours began with Robert Cooke and his successor, William Sherman at the Roosevelt Hospital in New York City where I was a medical resident. This direct lineage continues now into its fifth generation, and of course, we have many cousins in many other institutions. Our Cooke family tradition includes maintaining the practice of allergy within the mainstream of scientific internal medicine and pediatrics.

Another contribution closely tied with this lineage was the creation with **Elliott Middleton, Jr., MD, FAAAAI**, of *Allergy: Principles and Practice*. Thirty years ago the Mosby Company approached Elliott, also a graduate of the Robert A. Cooke Institute of Allergy, to write an allergy textbook, and Elliott asked me to join him. As we began planning the outline and selecting authors of the book we quickly realized we needed collaboration with a pediatrician, and **Eliot Ellis, MD, FAAAAI** agreed to be a co-editor. The success of *Allergy: Principles and Practice*, now in its sixth edition, as a reference source for the rapidly growing scientific information in our field confirms the value of this particular academic contribution.

The difficulty in selecting a particular research contribution is that the interesting questions that seemed clear and straightforward at the time have turned out to be exceedingly complex. Simply confirming one specific hypothesis about pathogenesis does not mean that the pathogenesis of a complex problem has been defined. Many other hypotheses may also be true. In the 1960's one of my interests was airway hyper-reactivity and Andor Szentivani's hypotheses that it was due to beta-adrenergic blockade, by some abnormality similar to the effect of pertussis toxin inactivation of the Gi signal transduction pathway that produces cyclic adenosine monophosphate. Many studies, both in my laboratory and others, confirmed that asthmatic subjects did have reduced physiological and cellular responses to beta agonists. But this reduced response has turned out to be the result of a number of different mechanisms including:
1. Internalization of the receptor by beta agonist activity. This internalization is promptly reversed by glucocorticoids; 2. Genetic differences in the beta-adrenergic receptor;
3. Inactivation of the receptor by eosinophil major basic protein; 4. Competition of Gi stimulation by Gs signal transduction by protease activated receptors stimulated by exogenous and endogenous proteases. The mechanisms of airway hyper-responsiveness are even more complex. In addition to the reduced response to beta agonists they include two different geometrical effects of airway inflammation, inactivation of muscarinic receptor 2 by eosinophil major basic protein, desquamation of airway epithelium, amplification of the response of airway smooth muscle by cytokines such as TNFa and IL-13, and several other mechanisms. What seemed simple when asthma was called "Hyper-reactive Airway Disease" has turned out to be very complicated indeed.

Over these past 50 years we have learned that asthma results from the interaction of many environmental agents (allergens, respiratory viruses, endotoxin, airborne irritants, etc.) with many different cells and receptors. The cellular pathways of many of these responses have genetic variability, for example HLA-2, that alters their response. Not only are there different genetic phenotypes, but also environmental exposure can influence gene expression. However it is clear that illness from environmental exposures follows a typical dose-response pattern.

One of my contributions has been development of methods of estimating the amount of exposure to allergens. This began with investigation of an epidemic of hypersensitivity pneumonitis in nylon producing plants in the 1970's. The cause was a contaminated cold mist air conditioning system. The organisms responsible for producing the antigens occur naturally in soil and lake water. After the source of exposure was identified and corrected, a critical aim became to monitor the air in the plant to be sure that the problem did not recur and the antigen concentration in the plant remained ho higher than outdoor air. To measure the concentration of antigen in the air, we applied a quantitative immunochemical assay to samples collected by a standard Environmental Protection Agency air-collecting device.

Mark C. Swanson and I have greatly improved the air sampling devices and the immunoassay methods, and applied the technique to many other occupational exposures. Within the limitations of allergen standardization we are able to estimate the airborne concentrations responsible for sensitization and for evocation of symptoms. It is also possible to determine the particle size and settling behavior of allergens. Several interesting results include confirmation that the asthma epidemics in Barcelona were due to soybean dust spreading over the city when ships in the harbor were unloading soybeans. Later these aeroassays also provided monitoring to assure that the dust emission was controlled. This assay technique has proved useful in identifying and controlling asthma from many occupational exposures. Also, it has helped clarify the paradox of asthma from pollens like ragweed. Pollen grains are too large to be respirable, and ragweed asthma becomes more severe after the peak of the pollen season is over.

By using Anderson samplers we found substantial quantities of airborne ragweed allergen only in particles the size of pollen grains, the exine, are stuccoed onto the pollen by other cells, the tapetum, that remain behind after the pollen is shed. A large amount of allergen remains in dead ragweed flowers even after snowfall. Interestingly we found more oak allergen in the air in August than during the May pollinating season. The source and clinical significance of this mid-summer exposure to oak allergen is still unknown. And in Tucson, Arizona, immunochemically detectable ragweed allergen is in the air all year.

Pollen allergy has turned out to be more complex (and therefore more interesting) than Blakley would have dreamed of in 1880. Contrary to the prediction of mathematical models indoor allergens settle at very different rates. Mite allergen settles very quickly; even the finest airborne particles have almost all settled within an hour of shaking the bedding. But cat allergen stays suspended; substantial amounts of even the largest particles remain in the air for 24 hours. The circumstances of how mite allergens, such an important cause of asthma, deposit in the airways still remain to be explained. I have also been interested in trying to determine a threshold limit value, that is the lowest concentration of airborne allergen that is required to provoke asthma. In both cat allergen exposure and several occupational exposures, we have found the concentration of allergen in the environment associates with symptoms to be much less, often ten-fold less, than the concentration required to produce a positive bronchial provocation test. In industrial exposures a concentration of about 1 ng/1 seems not to elicit sensitization, and 10ng/1 seems not to elicit symptoms in sensitized individuals.

One of the pleasures of retirement is reflecting back over what you have learned during your career. These 50 years have certainly seen our understanding of allergy develop enormously. It has been easier for my generation to master this body of information gradually as it developed than for our present trainees who have to learn it all in only two years. But this leisurely reflection generates many more new questions for the next generation to answer than my generation could have thought of. We answered the easy ones. The hard part is still to come.