

## Career interest turns toward allergic disease

By Samuel C. Bukantz, MD, FAAAAI

In 1932 (my junior year in Medical school), I was a substitute intern for two weeks at the Mount Sinai Hospital in New York City. During that time I had frequent contacts with Paul Klempere, Chief of Pathology, and Gregory Shwartzman, Chief of Bacteriology. That provided the stimulus for me to apply for a one-year internship in pathology and bacteriology to precede a three-year internship in medicine, all at Mount Sinai. During the internship in pathology and bacteriology, I isolated and characterized a gram-negative cocco-bacillus from a patient with sub acute bacterial endocarditis (*J. Mt. Sinai Hosp. 2:109;1935*).

Under Shwartzman's guidance, I immunized a rabbit with the organism and did agglutination absorption experiments which proved its similarity with an organism isolated and studied in Rochester, NY by Goldstein (*Am. J. Med. Sci. 187:672;1934*). This experience motivated a life-long interest in microbiology, immunology and the application of these sciences to the diagnosis and treatment of disease and ultimately to allergy and clinical immunology. During the latter part of my internship and residency at Mt. Sinai, I had successfully treated several patients suffering from pneumococcal pneumonia with specific anti-pneumococcal serum.

After completing the internship in 1938, I was appointed fellow in pneumonia research to Dr. Jesse Bullowa's service at Harlem Hospital in NYC. By that time, a considerable body of evidence had accumulated to indicate that *in vitro*, the bacteriostatic and bacteriocidal activity of sulfapyridine against the pneumococcus was superior to that of sulfanilamide. Sulfapyridine had also been shown to be capable of preventing or curing pneumococcal infection in a variety of animals and that the action is superior to that of sulfanilamide. This had been applied to the treatment of human pneumococcal infections.

Furthermore, a number of investigators reported that specific serum increases the anti-streptococcal and anti-pneumococcal activity of sulfanilamide both *in vitro* and in experimental infections. The studies of human infections had been done with Bullowa at the Harlem Hospital. There, specific anti-pneumococcal serums were provided by Lederle Laboratories to establish their safety and efficacy for FDA approval and release for clinical use.

In 1917 and 1918, Dochez, Avery and Blake had demonstrated the presence of soluble specific substance (SSS) of pneumococci in the blood and urine of patients suffering from lobar pneumonia. This was identified as capsular polysaccharide by Heidelberger and Avery and detected in the blood of 11 of 44 cases studied, 10 of whom died, the 11 having only traces in the blood. Blake demonstrated a reciprocal relation between the amount of polysaccharide in the blood and the development of antibody. At that time, Paul de Gara had emigrated from Austria and joined me and Bullowa at Harlem Hospital. We collaborated in the ongoing repetition of Blake, Dochez and Avery's observations.

We had obtained a photronreflectometer devised by Libby at Lederle Laboratories and had developed a sensitive titration of the precipitation of pneumococcal polysaccharide in an excess of specific antibody. The technique was then applied to study the comparative influence of sulfapyridine, specific serum, or the combination on the antigen-antibody balance in pneumococcal pneumonia and the relation to the outcome of therapy (*Ann. Int. Med. 14:1348;1941*).

Systematic determinations of capsular polysaccharide, agglutinin and precipitin titers were made on samples of blood of 135 patients with pneumonia caused by pneumococci types I, II, III, IV, V, VII and VIII in a series rotated for treatment with sulfapyridine, with serum, or with the two in combination.

Mortality of patients in whose blood capsular polysaccharide was present was 62.5% while the mortality of all the patients with bacteremia was only 29% and mortality for the entire series was 11.8%. Mortality for patients without bacteremia and without polysaccharide in the blood was only 3%. Of the 10 patients with serum positive form polysaccharide, and treated with sulfapyridine- six died. The illness of the four patients recovering under sulfapyridine therapy alone ran a prolonged course with a tendency to recurrence of fever, slow disappearance of capsular polysaccharide and failure to produce antibody. We demonstrated by these studies that specific antibody be administered to those patients in whom circulating capsular polysaccharide is detected so that the anti-immune effects of the latter could be neutralized.

At this time in 1941, I enlisted in the medical corps of the Army and three months later the United States entered World War II. The Medical Department Professional Service Schools (MDPSS) had added a program of vaccination with pneumococcus organisms to the existing prophylactic vaccination with typhoid and paratyphoid bacilli. I was assigned to the Army Medical Center and developed a vaccine containing the major types of pneumococci for prophylactic administration to American troops.

Because military personnel were increasingly exposed in malarious areas, we initiated studies to investigate the usefulness of serodiagnostic methods. Preliminary experiments resulted in the development of precise spectrophotometric methods for titrating the 50% hemolytic unit of complement and standardization of the hemolytic reaction. These methods were used in determining the optimal adjustment of reagents and conditions for a malaria complement fixation test (*Am J. Hyg.* 49:374;1949).

The program for testing antimalarials in prisoner volunteers, which was begun in 1944 by the National Institute of Health (*Am J. Hyg.* 47:113;1948), provided exceptional opportunities to evaluate the serologic test and to study the course of the CF reaction in sporozoite induced Vivax malaria in subjects infected with the St. Elizabeth's strain of p. Vivax. The course of the CF reaction was studied for eighteen months in each of 87 prisoner volunteers experimentally injected with sporozoites of the St. Elizabeth strain. Positive serologic reactions were associated with all but four of their 199 malarial attacks. The exceptions occurred only in primary attacks in which the tests became positive on the average 7.2 days after patent parasitemia and 6.2 days after fever. The parasitemia disappeared within 4-5 days after the initiation of therapy.

We concluded that the CF test for malaria might be helpful in identifying well-developed or recently subsided vivax infections. It would not be useful in diagnosis either early in an attack or during the long latent period between early and late activity. During the course of these studies I also developed a method of preserving sheep blood in Alsever's solution. The preserved erythrocytes retained normal responsiveness in complement fixation for months thereby reducing the frequency of bleeding sheep for the reaction.

Military personnel were also being exposed to possible tick transmitted infections in typhus endemic areas. Accordingly, we undertook a collaborative study with Canadian investigators to develop an anti-typhus vaccine. *Rickettsiae prowazeki* were cultured in eggs, the yolks of which were harvested to make the vaccine. The harvested yolks were purified to rid them of egg content and obtain the *Rickettsiae* in saline suspension. The absence of egg allergen in the final vaccine suspension was determined by applying skin tests with the vaccine in egg sensitive subjects or in skin sites of normal individuals passively sensitized to egg proteins. Final approved vaccines were administered to all military personnel who were sent to typhus endemic areas.

Stimulated by these experiences with immunologic principles and by a close friendship with the Chief of Allergy at Walter Reed Hospital, my interest then turned toward allergic diseases. Upon discharge from the military in 1945, I obtained a fellowship in allergy at Washington University under Harry Alexander, Chief of Allergy and Barry Wood, Chairman of Medicine. In collaboration with Harry Alexander, Stanley Hampton and Mary Johnson, colorimetric absolute methods were developed to analyze factors affecting deterioration of ragweed and other pollen extracts and establishing the prevention of their deterioration by glycerin. (*J. Allergy* 20:1;1949).

Studies with **Frank J. Dixon, MD, FAAAAI, David W. Talmage, MD, FAAAAI**, and Gustav Dammin then established that antigen elimination from the blood was an early manifestation of an immune response. Additional studies with radioactively labeled globulins indicated that the labeled proteins are handled much like the animals own globulins until antibodies to it are formed. After appearance of antibody labeled protein antigens are removed rapidly and catabolized. Antibody production, although initiated in the presence of antigen, continues long after antigen has disappeared.

Experience gained in these investigations were applied to the use of adrenocortical steroids in treatment of allergic disease. An important principle underlying safe therapy with steroids is familiarity with the major complications of that therapy and their mechanism, prevention and management. With such complications kept in mind, courses of steroid therapy were given to 39 allergic children and 13 adults for periods ranging from one to more than six months. The treatments were effective and complications, under the close surveillance of the patients, were exceedingly few. The studies demonstrated that steroid drugs may be safely used even for long term management, provided: 1) patients are kept

under close surveillance and, 2) the mechanism of complications are constantly kept in mind with appropriate clinical and laboratory observations performed to detect them at the earliest possible moment. (*JAMA 165:1256-64;1957*).

In 1958, I was appointed Clinical and Research Director of the Children's Asthma Research Institute and Hospital (CARIH) which had just been established on the grounds of the Jewish National Home for Asthmatic Children in Denver, CO. I was also appointed Associate Professor of Medicine at the University of CO on recommendation of Robert Glaser, my former colleague at Washington University and now Dean of the medical school in Denver. At CARIH, I was able to assemble a fine faculty, including **Teruko Ishizaka, MD, FAAAAI** and **Kimishige Ishizaka, MD, FAAAAI** for whom we established a well equipped research laboratory as well as a clinical service for the 150 intractable asthmatic children under our care.

In the succeeding several years, the Ishizakas, with the capable assistance of Margaret Hornbrook, my former research associate in Washington, DC, isolated and identified Immunoglobulin E as the antibody conveying allergic sensitivity. During my five years of residence in Denver, we did many studies of the use of corticosteroids for the treatment of children's asthma.

Simultaneously, we established a faculty of psychiatrists and psychologist who did many careful studies of the patients and their family members in the effort to identify and treat the psychogenic mechanisms aggravating asthma in the patient population.

In 1972, I joined the Department of Medicine at the University of South Florida in Tampa as Professor of Medicine and Chief of the Division of Allergy and Clinical Immunology. **Richard F. Lockey, MD, FAAAAI** joined the Division in the following year as Associate Director and became Director in 1983 and has had the major influence in the training, clinical, and research activities developed by this respected facility.