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Abul Abbas: An epitome of scholarship

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ABSTRACT

Immunology is a relatively new specialty. Ironically, the immune system impacts every physiological system in the body, but yet most textbooks of physiology do not include any functional aspects of the immune system. Indeed, with the exception of early descriptions of anaphylaxis and allergy, the majority of immune studies were focused on either the anatomy of lymph nodes and spleen, or of course on protection from microorganisms. The concept of autoimmunity is even newer and the first textbook on autoimmune disease was not published until 1963. For the past 50 years however, autoimmunity has virtually exploded from a field populated by a few, to recognition that autoimmune diseases can affect more than 10% of the population. There are many people that have contributed to this information explosion and the Journal of Autoimmunity devotes specific issues in recognition of the select few scientists that have contributed in a way that impacts not only their research peers, but also, and more importantly, the patients who suffer from autoimmune disease. Abul Abbas is one such individual. Abul is known not only for his outstanding research, but for his role in teaching and public service. His own scientific work is extraordinary and his impact is felt throughout the world. In this special issue a number of Abul's colleagues have specifically written papers to honor this unique individual. It is an extraordinary honor to be chosen for a special issue of a journal in recognition of one's career.

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1. A career of balancing research and education

Abul Abbas was born in a city in India, Patna, on the banks of the Ganges River. He was educated in a wonderful boys' school run by Irish-American Jesuits. After high school and a year of "college pre-med" (a typical path in India then), Abul entered the All-India Institute of Medical Sciences (AIIMS) in Delhi as a medical student. The AIIMS was (and, in many ways, still is) a remarkable institution because in a country steeped in the idea of doctors being healers, this school was created to emphasize that medicine had to be founded on scientific principles. Another unusual feature of the AIIMS was that it was a residential university with a small class size, meaning that all of the fifty students in each class had to live on campus. The approximately 6 years Abul spent there were some of the most enjoyable in his life. He learned an amazing amount, and forged lifelong friendships and a loyalty to the institution that stay to this day. Those years also convinced him that his interest in Medicine lay more in understanding the workings of the human body than in treating ill patients. At the AIIMS, Pathology was one

of the most impressive departments, with the best teachers and the greatest emphasis on disease mechanisms. It was, therefore, not unusual for students interested in the science of medicine to choose the discipline of Pathology as their careers. After completing medical school, Abul, like many of his classmates, applied for residency programs in the US. He was incredibly fortunate to be accepted into the Pathology program of the Peter Bent Brigham Hospital in Boston (now the Brigham and Women's Hospital), and in 1970 started the training path that would shape his career.

2. Clinical and research training in Boston

Residency training at the Brigham was an eye opener for many reasons. Abul was exposed to the clinical discipline of Pathology, and its essential role in diagnosis and patient care. But even more importantly, he saw first hand the process of scientific investigation and began to develop his interest in Immunology. The Brigham was renowned for studies of renal diseases and graft rejection. And, being located across the street from the Harvard Medical School (HMS) campus, it was influenced by the extraordinary growth of Immunology at HMS, spurred by the arrival in 1970 of future Nobel laureate Baruj Benacerraf as Chairman of Pathology. He started to teach himself Immunology, spending many evenings in the

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Countway library of HMS with review articles, and going to all the seminars he could attend. It wasn't all work, because he met his wife (also a resident then) at the Brigham!

When he finished three years of clinical training, he was very fortunate to be accepted as a research fellow in a joint program directed by Morris Karnovsky and Emil Unanue at HMS. The project involved defining the cellular distribution of important lymphocyte surface molecules, using immunofluorescence and electron microscopy techniques. Perhaps the most important aspect of the project was that he learned the principles and rigor of the scientific process – how to design experiments, and analyze and interpret results. And he was exposed to some of the brightest young minds in Immunology, who were defining the basis of MHC restriction and lymphocyte activation.

It became clear that he needed another research fellowship, to learn new ideas and approaches. In those days, many young immunologists were going to the National Institute for Medical Research at Mill Hill in London, where some of the most exciting discoveries in Immunology were being made. He was accepted as a fellow in the laboratory of Gerry Klaus and John Humphrey, and his wife and he moved to London in 1975. The two years he spent at Mill Hill were among the most formative of his training as an immunologist. The approach in England then was to let fellows follow their own paths, with minimal guidance. He became increasingly focused on the mechanisms of B cell tolerance, leading to an interest in immunological tolerance that continues to this day.

The years at Mill Hill were priceless for another reason. Abul was in the habit of coming to the lab by 8 or so in the morning, and the janitors were unhappy about this because he was in their way as they were cleaning the floors. So he got into the routine of taking a cup of coffee to the beautiful library at Mill Hill and spending an hour or two reading a different Immunology journal each day. It proved to be an amazing learning experience, and was critical in developing his interest in the discipline.

In his second year at Mill Hill, Ramzi Cotran, who had been recently appointed Chair of Pathology at the Brigham, was visiting London and dropped by to see Abul's lab. As he was leaving, he asked if Abul wanted a job when he returned to the US. Since this was the only offer he had ever received, he accepted with alacrity, with a handshake and no written contract or letter! It was years later that he fully appreciated what an opportunity Ramzi had given him.

3. On the faculty at the Brigham and Harvard

Starting a lab in Boston with one technician and one NIH grant was quite exciting. Emil Unanue welcomed him as an "honorary" member of his research group, and he found a forum to present data as well as an invaluable person to turn to for scientific advice. Ramzi Cotran was his other key mentor, who taught Abul to navigate the academic terrain and the value of mentoring young trainees. The Brigham then was perhaps the country's leading academic Pathology department, and Ramzi's influence is still apparent in the nearly two dozen Department Chairs nationally who were residents or faculty members in his department. His death in 2000 was a tragedy for the discipline and for the countless individuals who benefited from his wisdom and guidance.

Abul's research program grew quite rapidly, in large part benefiting from collaborations with some extraordinary colleagues at Harvard. His focus remained on cellular interactions in immune responses. Several projects merit highlighting.

- With Ken Rock, now Chairman of Pathology at the University of Massachusetts Medical School, they showed that B cells used their antigen receptors to bind and internalize protein antigens

and display peptides for recognition by helper T cells. Their finding that B cells presented antigens they recognized at 10^4 lower concentrations than antigens that were not bound by the receptor was the key to establishing the unique role of B cells as specific antigen-presenting cells [1]. Shortly after their paper was published, Antonio Lanzavecchia's lab published much the same finding in an elegant study using human B and T cells.

- Andrew Lichtman, then a postdoctoral fellow in Abul's lab and now a Professor of Pathology at HMS, was among the first to discover that different T cell clones used IL-2 or IL-4 as their autocrine growth factor [2]. This result came soon after the discovery of Th1 and Th2 subsets by Mosmann and Coffman, and led to a long interest in the functions and biology of these subsets. They went on to demonstrate that Th2 cells were more potent helpers for certain antibody responses [3].
- Using transgenic models that were pioneered by Marc Jenkins, they became very interested in the control of T cell tolerance and apoptosis. They showed that Fas was involved in peripheral deletion of T cells but not in their selection in the thymus [4]. Later, they showed that the inhibitory receptor CTLA-4 was involved in the induction of tolerance in T cells. These results led to the conclusion that different self antigens may exploit different pathways of tolerance, an idea that continues to fascinate them even today.

As the research program developed, Ramzi embarked upon an impressive expansion of the Brigham's Pathology department, coinciding with an explosive growth of the institution. By 1990–91, Abul was promoted to Professor at Harvard, and made the Head of the Immunology Research Division in the Department of Pathology at the Brigham. At their peak, they had five faculty members in the Division, with over 60 fellows, graduate students and technicians. The floor-wide lunchtime lab meetings on Wednesdays were exciting, and an incredible learning experience for all of them. It was especially thrilling to see new scientific results emerging, such as the discovery in the lab of Arlene Sharpe, a faculty member in the Division, that germline deletion of CTLA-4 resulted in lethal autoimmunity. Those years at Harvard also led to many lasting friendships, both personal and professional for Abul. In addition to people he mentioned earlier, Steve Burakoff, Ron Germain, Vijay Kuchroo, David Hafler, Shiv Pillai are a few of the friends he made who remain close after all the years.

4. An increasing interest in education

The two decades Abul spent as a faculty member at Harvard were also critical for developing his interest in teaching. He had enjoyed teaching medical students even when he was a Pathology resident, and upon returning to the faculty, he was asked to become one of the three principal faculty members for the Pathology course of the newly launched MD program in Health Sciences and Technology (HST). The HST program was started as a joint endeavor between Harvard and MIT, designed to teach medical students the quantitative and scientific basis of medicine. Although his personal quantitative abilities are decidedly suspect, he found HST students very stimulating because of their passion for science. During the Pathology course, he gave 5 lectures on "Immunopathology", which was the only Immunology that the HST program taught in its early years. It quickly became quite obvious that 5 lectures were inadequate, and the HST curriculum committee decided it was time to start a stand-alone Immunology course. From this, a new course called "Cellular and Molecular Immunology" was started in the mid-1980s. This course became an important part of Abul's academic life, and a source of great personal satisfaction and enjoyment. Subsequently, Andrew Lichtman took over as Director of this

course and Abul became increasingly involved in the Immunology course for the main HMS medical education pathway. Many of his views about how and what to teach, and what students do and do not appreciate, evolved during these years as Abul was participating in Immunology and Pathology courses at HMS.

Writing textbooks has been another major part of his professional life. How he got involved in this was truly fortuitous. In the late 1980s, Abul was contacted by an editor at W. B. Saunders (now Elsevier) with the suggestion to write a textbook of Immunology. The first edition of their book *Cellular and Molecular Immunology*, written by the three faculty members for the HST Immunology course then (Andrew Lichtman, Jordan Pober and Abul), was published in 1991. In the last 20+ years, the book has gone through eight editions, and Shiv Pillai has joined Andy Lichtman and Abul as a co-author. The most satisfying aspect of the book, and of teaching Immunology, has been the evolution of the science. Immunologists now understand most of the basic mechanisms of immune responses, and are able to utilize the knowledge to develop therapies for vexing diseases. These are accomplishments that all scientists in the field can be proud of.

In 2000, they realized that more and more medical schools were developing integrated curricula, and Immunology courses were becoming 2 or 3 weeks long. This led to a second much smaller book, *Basic Immunology*, an attempt to present fundamental principles and their clinical relevance in a concise and simple way. Abul and his colleagues became increasingly interested in developing short courses that might be useful for clinicians and investigators in companies and academia who needed a refresher in Immunology and its clinical applications. Over the last ten years, they have developed such 1–2 day courses and given them at many conferences, and in academic institutions and pharma companies. The positive responses they get for their textbooks and courses remain a source of enormous satisfaction.

5. The move west: the years at UCSF

It was a true pleasure when in 1999, Abul was offered the position of Chair of Pathology at the University of California San Francisco (UCSF). The move led to a great deal of anxiety, because he and his wife knew very little about California and their two children were on the east coast. But UCSF has more than lived up to his hopes. The Department of Pathology has an extraordinary collection of faculty and trainees, and together they have been able to build what they immodestly feel is one of the leading academic research-intensive Pathology departments in the country. The Immunology program at UCSF has grown remarkably in the last decade, in concert with the growth of the entire institution. Abul's colleagues in Immunology have been wonderful collaborators and personal friends; he has many of these at UCSF, to name only a few (in alphabetical order) Mark Anderson, Jeff Bluestone, Tony DeFranco, Lewis Lanier, Cliff Lowell and Art Weiss. He has also been fortunate to have some outstanding research fellows in his group at UCSF – Lucy Walker, Hans Doms, Birgit Knoechel and Jens Lohr in the early years, and Iris Gratz and Mike Rosenblum recently. Because of them, and many other excellent students and research fellows, their research programs have moved in new directions, especially emphasizing the balance between pathogenic and protective T cells [5], the role of IL-2 in the control of immune responses, and the concept of regulatory memory in tissues [6].

Abul's involvement with textbooks took a leap when his close friend Vinay Kumar, Chair of Pathology at the University of Chicago, asked Abul in 2002 to join him as one of the lead authors of the Robbins series of Pathology books. It was quite thrilling for him to be a co-author of a book he had read as a medical student. The last decade of involvement with the Robbins Pathology books have

been a great learning experience for Abul, thanks to Vinay and their third co-author, Jon Aster from the Brigham. It is also a testament to the late Stanley Robbins that these books retain their near-iconic status among medical students after almost fifty years!

6. Involvement with FOCIS

In the late 1990s, Abul's good friends Garry Fathman at Stanford and David Hafler, then at Harvard and now Chair of Neurology at Yale, spearheaded the establishment of a new organization, the Federation of Clinical Immunology Societies (FOCIS). The idea was revolutionary in many ways. It was founded on the view that physicians and scientists engaged in treating and studying diseases of the immune system had a lot in common and was not well served by their clinical specialties. In other words, the rheumatologist involved with rheumatoid arthritis shares her/his interests with the gastroenterologist looking after patients with inflammatory bowel disease, the dermatologist treating psoriasis, and so on. And if medicine is to develop a new taxonomy based on disease mechanisms and therapeutic strategies, it has to get beyond the silos created by clinical specialties. FOCIS was an attempt to achieve these goals around diseases affecting the immune system. It was also unusual in that it was a federation of existing societies and not an independent society of its own. Abul was involved with the creation of FOCIS, and especially with its education programs, from the outset. For the last two years Abul has been the President of the organization, and it has been especially gratifying for Abul to see how much recognition it gets worldwide and the new initiatives that are being launched.

7. Concluding remarks and impact

It is impossible to overestimate the impact Abul Abbas has had on the lives and careers of his students and his colleagues and obviously including his seminal work that has influenced so many others in many fields. Abul's work on the diversity of T lymphocytes is classic and one such paper has been cited more than 4000 times [7]. Indeed, it is nearly impossible to read recent data on autoimmune disease without appreciation of the implications of immune regulation, whether it be experimental models of myasthenia gravis, humans with dermatomyositis or lupus, children with juvenile arthritis, Sjogren's syndrome, basic science on the gut and the inflammatory response, the plasticity of the repertoire and burgeoning fields of proteomics, epigenetics, and metabolomics [8–30].

Abul Abbas has had a special relationship to autoimmunologists. He has graciously taught an introductory course on immunology to students that have attended the various Congresses of Autoimmunity. These courses have been described with terms such as “extraordinary,” “superlative,” and the “best I've ever attended.” I've witnessed Abul addressing even the most unsophisticated question with humility and patience. This is not surprising given the numerous honors and awards he has received for teaching, including excellence in teaching awards from the Harvard Medical School, invited memorial lectures at the Cleveland Clinic, the University of Rochester, the University of California School of Medicine at Los Angeles, the University of Texas, and including receipt of the Robbins Distinguished Educator Award from the American Society of Investigative Pathology. It is also not surprising given his editorial board service for the Journal of Immunology, the American Journal of Pathology, Immunity, the Journal of Clinical Immunology, Journal of Autoimmunity, Cell, the Annual Review of Pathology and the Journal of Clinical Investigation. This special issue and the distinction that is given to Abul Abbas belongs to a select few previous honorees, including Ian Mackay, Noel Rose, Hari

Moutsopoulos, Pierre Youinou and Chella David [31–33]. Finally, we will cite for completeness a small number of his contributions, as they are so reflective of a life devoted to research [1–3,5–7], [34–60], [61–90], [91–117]; truly an epitome of scholarship.

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