Obituary Anthony (Tony) Allison American J. Transplantation, 2014

On February 20, 2014 Anthony (Tony) Clifford Allison died from the complications of end-stage pulmonary fibrosis in his home overlooking the Belmont Valley near San Francisco. Tony Allison was once described as a scientist "who should have been known much better". And indeed for anyone who had the opportunity to meet him, work with him and know his scientific opus it was clear he was one of the most brilliant scientists of the 20th century. Allison's interests covered so many areas of Biology and spanned more than 60 years as a productive scientist. I regret to have to restrict myself, for the purpose of this obituary, to his work related to Transplantation.

I met Tony in late 1988 when he visited me in Wisconsin to whet my interest to collaborate with him to test a new Immunosuppressant called RS-61443. Prior to his visit he sent his Curriculum Vitae and it became instantly clear to me that I was going to meet with a preeminent scientist. As that time he was the Vice President for Research at Syntex (Palo Alto) and he had a long-time interest in purine metabolism (Lancet 1975, Dec 13). He had recognized that drug shelved by Lilly for treatment of lymphoma, mycophenolic acid (MPA), was both a powerful inhibitor of inosine-monophosphate-dehydrogenase and, more importantly, this inhibition was rather selective controlling synthesis in the *de novo* pathway for T and B lymphocytes. After several years of *in vitro* studies he and his wife Elsie Eugui in collaboration with Chemist Peter Nelson devised a more bioavailable and tolerable prodrug making the morpholino ester of MPA. The drug was given first the compound number RS-61443, then the descriptive name mycophenolate mofetil and finally the brand name CellCept®.

During his first visit I convinced him it would be worthwhile to perform a pilot study in a dog kidney transplant model and we agreed to bypass a rodent system. (Only later did I find out that he was already collaborating with Randy Morris using the ear heart model). Our initial experiments with higher doses of RS-61443 resulted in unacceptable gastrointestinal complications, but we did see some graft prolongation. This initial encouragement led us to gradually reduce the dose of RS-61443 and add small doses of cyclosporin A and prednisone. This formula was successful in the dogs. Two early clinical studies were done in patients. One study was done in kidney transplant patients with refractory rejection. The positive outcomes seen in this trial convinced Syntex to pursue the drug for solid organ transplantation. The other study was conducted using *de novo* renal allograft recipients. The dose-response reduction in acute rejection seen in these 16 patients became the basis of the three pivotal trials used for approval. With these initial findings in hand, the clinical trials progressed with unusual speed. In June of 1995 the CellCept was approved by the FDA and has become one of the commercially most successful drugs in the history of transplantation and a mainstay of the regimen.

The development of CellCept was just one of Tony’s seminal contributions. In my view, even more important was his discovery that individuals carrying the sickle cell gene were resistant to malaria (Br Med J 1954,Feb6). This was perhaps the first demonstration of Darwinism applied to a large population and gave rise to the concept

of a Balanced Polymorphism. It is of interest that Peter Medawar, in the view of many, unjustly refused to give credit to Allison for this landmark observation made when he was a student visiting his native Kenya during summer vacation. In addition, Tony suggested to a young Oxford-trained medical geneticist that the way to discover new and important antigens would be to screen serum samples from populations around the world against the serum of a multiply transfused patient. This technique allowed Baruch Blumberg to discover the Australia antigen, now known as hepatitis B surface antigen. Blumberg won the Nobel Prize for this discovery.

Dr. Allison was also one of the first who confirmed in a rabbit kidney transplant model the powerful graft prolonging effect of Cyclosporine A (Lancet 1978, June).

Much could be said about Tony Allison the person. He grew up in Africa and greatly admired and supported Nelson Mandela and Bishop Tutu. Later he spent a long period of his career in England but ultimately decided in favor of the Californian climate. Tony Allison was the embodiment of the Renaissance man. He was an expert bird watcher, music lover, wine connoisseur and knew much about deep-sea fishing. The first dinner he and I shared was at a famous Fish Market restaurant in Palo Alto. We ordered swordfish. The broiled fish tasted fine to me. Tony took one bite and called the waiter over to our table. He explained that this swordfish had been caught with a net (instead of a spear). The long struggle before death caused lactate accumulation. This created a bitter taste in the meat which Tony's refined palate detected. Minutes later an apologetic chef emerged from the kitchen and confirmed Tony's deduction.

Yes, Tony not only knew a lot about many subjects but his knowledge in these fields was extensive and deep. I will always be grateful that he sought me out to collaborate with him on the CellCept story. He could have asked dozens of young surgeons, but in the end it all worked out well for both us and our patients. Rest well, Tony. Yes, Tony, you should have been known a lot better.

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