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## The Importance of Having .Gamma

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Some months ago I was sitting in my small office with two venerable colleagues and friends. One was Alvin Friedman-Kien, a dermatologist, clinical virologist and art collector. For better or worse, Alvin and I have maintained a professional association and personal friendship since our early days at NYU only God knows how many years ago. The other was Joseph Sonnabend, an infectologist, interferon pioneer weaned in Alick Isaacs' laboratory, and music lover. I have known Joseph since the early stages of my career back in Czechoslovakia about 100 years ago. Joseph and Alvin have lately shared an interest in Kaposi's sarcoma. Not the rare, relatively benign form of this disease described by Moritz Kaposi, the smart Viennese doctor of Hungarian extraction, but the more modern version that has recently emerged with alarming frequency among younger homosexual men in New York and some other urban centres in America. Alvin has probably seen and treated more of these Kaposi's patients than anybody else in the world (Friedman-Kien et al.1981,1982).

During the meeting in my office Alvin and Joseph discussed some of the clues revealed by initial clinical and laboratory studies of Kaposi's patients. All of the patients were homosexual or bisexual, and a great majority had a history of drug abuse and multiple venereal diseases. Laboratory findings included high levels of antibodies to cytomegalovirus and Epstein-Barr virus. Alvin was very excited about some

immunological parameters observed in these patients by Pablo Rubinstein at the New York Blood Center. One of the findings was the presence of an unusual antibody on the surface of the patients' lymphocytes. This could be an auto-antibody reacting with an antigenic determinant of lymphocytes ...

At this point our discussion was interrupted. Alvin had to answer one of his numerous phone calls and I too had to leave for a little while. When I returned, Joseph was engrossed in reading the reprint of one of our recent papers showing that OKT3 monoclonal antibody specific for a cell surface component of human T lymphocytes was a potent inducer of interferon- $\gamma$  in cultures of human peripheral blood cells (Pang et al., 1981). Joseph was quick to point out that the antibody reacting with the lymphocytes of Kaposi's patients also might induce interferon. If so, then it should be possible to detect the interferon in the patients' serum.

An instant collaboration was started. Joseph provided the idea, Alvin supplied the patients' sera, and I furnished Dorothy Henriksen. Dorothy is a technician and part-time graduate student who along with many other skills has a knack for detecting and identifying interferons. As she was assisted in this project by Gene DeStefano, a congenial technician and student, success was virtually guaranteed.

Some weeks later it became clear that a high proportion of Kaposi's patients had interferon demonstrable in their sera. Another group of homosexual patients, who did not have Kaposi's sarcoma but showed multiple enlarged lymph nodes indicative of some underlying immune disorder, also had interferon in their sera albeit at a lower frequency. In contrast, none of the healthy homosexual men we examined had detectable interferon levels (Table V).

Neutralization tests with a set of specific antibodies revealed that interferon in (the sera of these patients was clearly of the  $\alpha$  type and not gamma as one might have expected on the basis of Joseph Sonnabend's original idea (Table VI). However, this finding actually fits quite well the emerging concept of an auto-immune disorder as the underlying cause of Kaposi's sarcoma and a handful of opportunistic infection (e.g. *Pneumocystis carinii* pneumonia, cryptococcal infections) occurring in the gay population. Enter systemic lupus erythematosus (SLE) ... <

The origins of the idea that interferon may be somehow involved in auto-immune disease can be traced back to Paris and Moscow. Working near the banks of the Seine (figuratively speaking), Ion Gresser and coworkers (Gresser et al., 1975, 1976) found that daily injections of newborn mice with large doses of interferon rapidly killed all treated animals. Injection of newborn mice with sub-lethal doses of interferon, on the other hand, produced months later a severe glomerulonephritis with deposits of immunoglobulins and complement. Meanwhile in the Soviet capital, Simon Skurkovich with his Russian colleagues (Skurkovich et al., 1974; Skurkovich and Eremkina, 1975) published several studies suggesting that "hyperproduction of interferon" was involved in the pathogenesis of allergies and auto-immune disorders. Although in one of the papers Skurkovich et al. (1974) described the presence of interferon in the serum of SLE patients, no one seemed to be paying attention. (Some years later Simon Skurkovich entered the ranks of Soviet refusenik scientists and he now lives and works in the United States.)

Only after the group from Abner Notkins' laboratory

(Hooks et al., 1979) published results of an extensive study ("Immune Interferon in the Circulation of Patients with Auto-immune Disease") did the research community start to pay some attention to the association between interferon and auto-immune disease. Sera from 28 SLE patients were examined and almost half of them contained demonstrable interferon. Patients with other autoimmune disorders (rheumatoid arthritis, scleroderma, Sjogren's disease) also had a high incidence of positive serum interferon levels. Pointing out the numerous known immunoregulatory activities of interferon Hooks et al. quite cautiously concluded: "Thus, it is possible that the immunologic abnormalities associated with systemic lupus erythematosus, such as hypergammaglobulinemia, autoantibodies, immune complexes, decreased lymphocyte blastogenesis and decreased suppressor-T-cell activity, may be in part mediated by circulating immune interferon." Still, despite the enormous interest in the pathogenesis of SLE, there was no mad rush of former and future Nobel prize winners into the field of interferon and auto-immunity ...

My own involvement in this area started in the spring of 1981 with a phone call from another venerable colleague and old friend, Robert Friedman. Bob - a distinguished NIH virologist, pathologist and world traveller - was working with Olivia Preble on the characterization of the interferon found in sera of patients with SLE. Hooks et al. (1979) had originally concluded that it was "immune" or  $\gamma$  interferon. This conclusion was based on the observed inactivation of the interferon in patients' sera after exposure to pH 2. Loss of activity on exposure to pH 2 is considered one of the hallmarks of interferon-

