

# Henry G Kunkel and Rheumatoid Factor

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Henry Kunkel was born in Brooklyn, New York in 1916. He died in 1983 at the early age of 67. He was an outstanding clinical scholar who had a deep passion for scientific facts. Almost all his scientific life was involved in biomedical research at the Rockefeller University in New York City. He had a laboratory on the third floor of Founder's Hall (the first building at what was then Rockefeller Institute for Medical Research). His office was a spare, unpretentious room with a view of the East River in Upper Manhattan. To this room came many scientists the world over as well as many of his former fellows who came back to see the old master. He was especially glad to talk about experimental data and would drop what he was doing to talk about the deeper significance of their observations. His parting words would often be, 'Come again'

Kunkel has received numerous accolades which could be exemplified in the following story. His research grant application was being reviewed at an NIH Study section meeting and a reviewer pointed out the lack of details concerning techniques and procedures, but also said and I paraphrase, 'but he (Kunkel) knows that we know that he knows how to do it.' The application sailed smoothly through the meeting.

## 19S RHEUMATOID FACTOR IS ANTIBODY TO IMMUNE COMPLEX

Among all the outstanding work that Kunkel has done, I consider his studies on the characterisation of rheumatoid factor (RF) to be a trailblazer in making us become aware of the intricacy of interacting cellular functions which unexpectedly enable production of outcomes which are pathogenic. In the 1950s, Kunkel and his associates used a Spinco Model E analytical ultracentrifuge to study proteins of different sedimentation constants in serum. These studies culminated in two papers,<sup>1,2</sup> which described a population of proteins in rheumatoid arthritis (RA) sera with a high sedimentation constant of 22S. The 22S protein component was a complex of 19S and 7S proteins; the 19S protein was RF and the 7S component was identical to 7S gamma globulin. Further studies revealed that the 19S protein was like antibody in that many other immune complexes could bind to the 19S protein dissociated from the 22S complex. The proposal that RF might be an antibody to antigen-antibody complexes was completely novel and surprising and aroused much scepticism; further evidence that 19S RF isolated from the 22S complex had other properties of 7S gamma globulin antibody convinced the sceptics. In quantitative immunoprecipitation experiments, immunoprecipitates of 22S could be solubilised in zones of antigen excess. In an understated fashion, Kunkel and his associates said that, 'a search for the hypothetical antigen-antibody

complex giving rise to the RF might yield considerable further information.'<sup>2</sup>

## SYNOVIAL CAVITIES AND OTHER SEQUESTERED SITES MAY BE NIDUS FOR SUSTAINED ANTIBODY AND IMMUNE COMPLEX-MEDIATED INFLAMMATION IN RA

These seminal studies were suggestions that, to elucidate the pathogenesis of RA, one should include studies in which antibody and immune complex-mediated pathogenesis are involved. Many decades after the original observations, I believe we are beginning to unravel the complex scenario of RA pathogenesis. It is highly likely that the major candidate antigen in the 'hypothetical antigen-antibody complex' could be citrullinated filaggrin, a cytokeratin filament aggregating protein. Initially called perinuclear factor, it is produced by deiminating enzymes in many cell types.<sup>3-5</sup> As the Kunkel studies suggested, other antigen-antibody complexes may also be involved, but citrullinated proteins may be the major player. A renewable source of citrullinated proteins appears to be the synovial cavities of inflamed joints. Hollingsworth *et al*<sup>6</sup> showed that the high percentage of neutrophils in synovial effusions was due to high turnover and not due to stagnation of neutrophils in synovial cavities. As studies showed, in RA synovial fluid, the major chemoattractant factor is complement component C5a and neutrophilia is augmented by C4a, a chemotaxis inhibitor for monocytes, allowing the preferential accumulation of neutrophils.<sup>7</sup> The fact that complement-related fragments are plentiful in synovial fluids is a strong testament for the role of complement activation<sup>8-11</sup> and the membrane attack complex (C5b-C9) in inducing hypercitrullination of neutrophil intracellular proteins.<sup>12,13</sup> Basically, it can be said that the 'RF is antibody to immune complex' concept is the key to a reasonable construct on the chain of events in RA pathogenesis (also see detailed review in,<sup>14</sup> and RA is probably an extreme form of immune complex illness.

Henry Kunkel received numerous honours during his lifetime, including the Gairdner Foundation Award (1962), Doctor of Medicine (*Honoris Causa*) University of Uppsala, Sweden (1964), Modern Medicine Distinguished Service Award (1973), Albert Lasker Award for Basic Medical Research (1975), Passano Foundation Award (1975), Avery Landsteiner Award (1975), American College of Physicians Award (1975), Louisa Gross Horwitz Award of Columbia University (1977), New York Academy of Medicine Award (1977), Kovalenko Medal of the National Academy of Science (1979), Lita Annenberg Hazen Award (1980), Pasteur Medal (1980) and Doctor of Medicine (*Honoris Causa*) Harvard University (1982). The photo of Henry Kunkel (see figure 1) was taken in 1980 at a restaurant in Paris



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**Figure 1** This picture of Henry Kunkel was taken in 1980 at a restaurant in Paris on the occasion of a meeting of the International Congress of Immunology. He had just been informed that he was the recipient of the Lita Annenberg Hazen Award for Excellence in Clinical Research (from the personal collection of the author).

when he was informed that he had received the Lita Annenberg Hazen Award for excellence in clinical research.

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