Abstract
Rheumatoid factors are 9s IgM autoantibodies directed against the hinge regions of 7s IgG’s that have been changed consequent to their encounter with a foreign antigen, such as those produced by oral bacteria. Occasionally self-aggregating 7s IgG’s serve this function. When these complexes are taken up by phagocytes in the joint, they form the “RA cell,” a cell analogous to the LE cell of Hargraves. The circulating complexes, which activate complement cascades in the joint, are not specific for RA, being found in other rheumatic and autoimmune diseases as well as having a low prevalence in the normal population. Recently, other antigens resulting in autoimmune complex formation with greater specificity for RA have been described. These antibodies, known as anti-cyclic citrullinated peptide (anti-CCP) antibodies recognize citrullinated protein residues, which are present as antigenic determinants in patients with RA. This is in contrast to systemic lupus erythematosus (SLE), another autoimmune disease characterized by immune complexes in the systemic circulation. In the case of SLE, 7s IgG’s directed against several nuclear antigens localize mainly in the kidneys and blood vessels. They also produce cerebral and pulmonary disease by activating complement systemically. Genetic defects in the complement cascade associated with SLE result in inadequate clearance of immune complexes as well as apoptotic blebs containing autoantigens.

Rheumatology came late to the game of medical science and even later to immunology. From 1933 to 1948, our medical specialty was a descriptive art—we had no idea, in any meaningful way, what was going on. Cardiologists had their EKGs and digitalis, the endocrinologists had their thyroid tests and extracts, but rheumatologists seemed condemned to stand idly by to watch their patients turn into cripples or die in lupus crisis after one or another stopgap treatments. Oh yes, we had diathermy, gold salts, paraffin injections and, believe it or not, bee venom. We knew how to treat gout with colchicine, were just learning to give penicillin to prevent rheumatic fever, but by and large our treatment of joint disease or even systemic lupus erythematosus (SLE) was limited to aspirin, aspirin, and more aspirin. All that changed in the annus mirabilis of our field, 1948.

At a staff meeting of the Mayo Clinic in January of 1948, Malcolm M. Hargraves described a strange kind of cell that formed in blood samples of patients with SLE. Before 1950, we could not really tell who had SLE and who did not; we had “no clue” as to why SLE was so often fatal. Hargraves had discovered what he called the “LE cell,” which finally permitted us not only to make a diagnosis of the disease, but also told us what was going wrong with these poor women. The LE cell, it turned out over the years, is a white blood cell (a neutrophil) that has ingested the dying nucleus of another cell, against which lupus patients make antibodies. Complement was involved, acting as an opsonin. It also turned out that those antibodies against the nucleus and/or its constituents—the anti-DNA antibodies—were just the tip of an iceberg. SLE patients produce a dazzling number of antibodies, with their Fab regions directed against bits and pieces of their own cells. Their immune system recognizes such bits of “self” as if they were a microbe, a tad of “non-self” that wants expunging. Hargrave’s discovery of the LE cell sparked the study of autoimmunity and lifted rheumatology over the threshold of science.

Gerald Weissmann, M.D., is Director of the Biotechnology Study Center, New York University School of Medicine; Research Professor, Division of Rheumatology; and Professor Emeritus of Medicine, Department of Medicine, NYU Langone Medical Center, New York, New York.
Correspondence: Gerald Weissman, M.D., OBV 6 686, 462 First Avenue, New York, New York 10016; gerald.weissmann@nyumc.org.
In the same month, immunologist Harry Rose and rheumatologist Charles Ragan of Columbia described a factor in the serum of most patients with rheumatoid arthritis (RA) that clumped sheep red blood cells coated with human antibodies: the “sensitized sheep cell agglutination test.” Tests for this factor not only permitted accurate diagnosis of RA, but also taught us how joints are attacked in RA. What came to be called “rheumatoid factor” turned out to be yet another autoantibody, of great size and with a tendency to form sludge in the blood. Normal human antibodies, the “self” in this case, were recognized as “non-self” by rheumatoid factor. The agglutination reaction in a test tube was a pretty good reflection of what happens in life. In patients with RA, complexes of antibodies containing rheumatoid factor form in the blood like *iles flottant*; they become trapped in joint spaces, joint cells try to get rid of the unwanted debris, cry havoc, and let loose the dogs of inflammation: anaphylatoxins C3a, C5a, and eicosanoids, etc. As with Hargraves and the LE cell, the discovery of rheumatoid factor made it possible to make sense of yet one more of our diseases. Another finding, RA is an immune complex disease in which complement is activated, as Peter Ward and Nathan Zvaifler were the first to document. 

On April 20, 1949, William A. Laurence of *The New York Times* broke news of another discovery announced at a staff meeting at the Mayo Clinic: “Preliminary tests during the last seven months at the Mayo Clinic with a hormone from the skin of the adrenal glands has opened up an entirely new approach to the treatment of rheumatoid arthritis, the most painful form of arthritis, that cripples millions, it was revealed here tonight.”

That evening, Philip Hench, Charles Slocumb, and Howard Polley had reported their experience with 14 cases of RA treated with a precious material called “Kendall’s compound E,” or 17 hydroxy-11 dehydro-corticosterone. Cortisone had entered the clinic. Within a week, cinemas nationwide showed newsreels of cripples rising miraculously from their wheelchairs. By May of 1949, Hench and coworkers had reported the “complete remission of acute signs and symptoms of rheumatoid arthritis, the most painful form of arthritis, that cripples millions, it was revealed here tonight.”

On October 1950, the Nobel committee announced that Philip Hench and the two biochemists who had painstakingly isolated and described the chemistry of adrenal steroids, Thaddeus Reichstein (University of Basel, Basel, Switzerland) and Edward Kendall (Mayo Clinic, Rochester, New York, U.S.), would receive the Nobel Prize in Physiology or Medicine for “their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects.” Hench remains the only rheumatologist among Nobel laureates. So universal was the acclaim for cortisone that the Swedish announcement of the 1950 Nobel Prize in literature (Bertrand Russel) was almost a footnote in the world press.

Studies of how cortisone works its magic in RA and SLE led two generations of rheumatologists into the field. These studies contributed both to the basic science of immunology and to the treatment of patients with rheumatic disease. It must be admitted, however, that nothing we have learned since Hench’s Nobel Prize has given us any notion of what causes either lupus or RA. We have, however, learned much about how immune reactions mediate the pathology of RA and SLE. IgG/IgM complexes have been implicated in RA since the early work in Joseph Hollander’s lab. He explained the crucial experiments of 1965:

To test further our hypothesis of the immunopathogenesis of rheumatoid arthritis, we isolated gamma-G from rheumatoid serum and injected a few milligrams of this into an uninflamed knee joint of the patient from whom the serum was obtained. In every case, an acute joint inflammation developed within hours, but gamma-G from normal donors, prepared identically and in the same dose, caused no reaction in the contralateral knee at the same time. Rheumatoid gamma-G injected into osteoarthritic joints (seronegative for rheumatoid factor) produced no inflammatory response.

When such complexes are taken up by phagocytes in the joint, they form the “RA cell,” a cell analogous to the LE cell of Hargraves. The circulating complexes are not specific for RA, being found in other rheumatic and autoimmune diseases, as well as having a low prevalence in the normal population. Recently, other antigens resulting in autoimmune complex formation with greater specificity for RA have been described. These antibodies, known as anti-cyclic citrulli-

**Table 1** Comparison of Immune Complex Formation in the Autoimmune Diseases Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE)

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<thead>
<tr>
<th>Immune response</th>
<th>RA</th>
<th>SLE</th>
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<tr>
<td>Diagnostic “tell-tale” cell</td>
<td>RA cell (phagocytes with ingested rheumatoid factor complexes)</td>
<td>LE cell (phagocytes with ingested cell nuclei)</td>
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<tr>
<td>Antigen</td>
<td>Hinge region of IgG</td>
<td>DNA, histones, etc. phospholipids</td>
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<tr>
<td>Antibody</td>
<td>19s IgM, self-agg7s IgG</td>
<td>7s IgG</td>
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<tr>
<td>Antigen/antibody deposition</td>
<td>Synovium, cartilage</td>
<td>Kidneys, blood vessels</td>
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<tr>
<td>Complement activation</td>
<td>Synovial fluid C3a, C5a, C5b-9</td>
<td>Systemic C1q, C3a, C5a, C5b-9</td>
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nated peptide (anti-CCP) antibodies, recognize citrullinated protein residues, which are present as antigenic determinants in patients with RA. Mart Mannik had earlier found that some 7s IgG rheumatoid factors self-aggregate to form larger immune complexes via hydrophobic interactions to become trapped within the synovial tissue.9

This “complex-laden” setting is in contrast to that of SLE, another autoimmune disease characterized by immune complexes in the systemic circulation. In the case of SLE, 7s IgGs directed against several nuclear antigens localize mainly in the kidneys and blood vessels.10 They also produce cerebral and pulmonary disease by activating complement systemically.11 Genetic defects in the complement cascade associated with SLE result in inadequate clearance of immune complexes, as well as apoptotic blebs containing autoantigens.12

Table 1 summarizes the role of immune complexes in the two diseases. In RA, immune complexes cause local joint inflammation by activating complement but also stimulate phagocytes directly. Neutrophils, which comprise more than 90% of the total cell population in synovial fluid, take-up immune complexes via Fc receptors that trigger release of hydrolytic enzymes, the generation of reactive oxygen species, and products of arachidonic acid metabolism. These promote an inflammatory response or lead directly to tissue degradation, or both.13

We could say, therefore, that tissue injury in RA is due to a combination of phagocytes (innate immunity) and anaphylaxis (acquired immunity) gone awry. Immune complexes create their havoc via Fc gamma III receptors that signal via the tyrosine phosphorylation immunoreceptor pathway. Anaphylatoxins, mainly C5a, signal via the MEK/MAP kinase cascade, and both engage in cross-talk via NF kappa B. We now appreciate that cytokines, such as TNF alpha and IL-1, are important mediators of inflammation in RA,14 but in the joint they act downstream of the primary insults: immune complexes and anaphylatoxins. Many of the currently used and developing therapeutic strategies against RA are successfully targeted toward these cytokines, first appreciated as “lymphokines.”15 Others are directed toward the cell-cell interactions between subsets of T cells and B cells—and now of other antigen-presenting cells—that produce the auto-antibodies in the first place.

Although we have no clue as to the true etiology of either SLE or RA, we have dramatically changed the treatment of both diseases. The new biological agents and small molecules that curb rheumatic disease have resulted from decades of basic discovery made in the lab. We owe much to the pioneers of experimental rheumatology who have taught us the basic facts outlined herein: K. Frank Austen, Claude Bennett, Charles Christian, Frank Dixon, Edward C. Franklin, Joseph Hollander, Halsted Holman, Stephen Krane, Henry Kunkel, Mart Mannik, Hans Mueller-Eberhart, Lewis Thomas, John Vaughan, Morris Ziff, and Nathan Zvaifler.

Disclosure Statement
The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References