Blood Clotting and Coagulation Factors: The Work of Yale Nemerson

After developing a blood disorder, Yale Nemerson became interested in hematology. This led to his lifelong study of thrombogenic tissue factor and to his contributions to developing the modern theory of blood coagulation. The two Classic papers reprinted here detail some of Nemerson’s studies on coagulation factors IX and VII.

Kinetics of Factor IX Activation via the Extrinsic Pathway. Dependence of $K_m$ on Tissue Factor

The Dual Role of Factor VII in Blood Coagulation. Initiation and Inhibition of a Proteolytic System by a Zymogen

Yale Nemerson (1931–2009) was born in New York City. He attended the Bronx High School of Science and spent a semester as a tennis recruit at Tulane University before transferring to Bard College. (He was a superb tennis player and, in later years, took lessons from Roy Emerson who won 28 Grand Slam titles.) After taking time to travel and join the family real estate business, Nemerson decided to go to medical school at New York University to become a psychiatrist. However, after developing a bleeding disorder, he chose to focus on hematology. Nemerson received his M.D. in 1960 and did an internship at Lenox Hill Hospital and residency at Montefiore Medical Center. He then joined the laboratory of Theodore H. Spaet in 1962 and began a lifelong study of thrombogenic tissue factor, in which he helped to develop the modern theory of blood coagulation by establishing that tissue factor, bound to coagulation factor VIIa, is responsible for initiating the extrinsic pathway of thrombin formation.

After 2 years with Spaet, Nemerson joined the Yale University medical faculty and quickly rose to full professor. He focused on understanding the mechanics and role of tissue factor using material from a small herd of cows in a town near New Haven. In 1975, Nemerson moved to Stony Brook University to build what he hoped would be one of the premier hematology departments in the world. However, budget cuts throughout New York State dished his plans, and he moved to Mount Sinai Medical School in 1977. Eventually he became the Philip and Harriet Goodhard Professor of Medicine. Nemerson remained as Professor Emeritus of Medicine in the Division of Hematology and Medical Oncology at Mount Sinai until his death in 2009.

Nemerson’s earliest studies, with Frances Pitlick, showed the tight association of tissue factor to phospholipids. In the early 1970s, he began a collaboration with Jolyon Jesty, Robert Radcliffe, and Sidonie Morrison and was able to purify factor VII, develop an accurate method...
for measuring factor Xₐ generation, and demonstrate the critical feedback activation of factor VII by factor Xₐ. Later, Nemerson purified human tissue factor, which led to the cloning of its cDNA and the solution of a high resolution crystal structure of the tissue factor-VIIₐ complex. Nemerson also developed a novel system for studying the kinetics of the tissue factor pathway under flow conditions and shear rates comparable to those in the vascular system. This model allowed his group to present evidence that tissue factor in blood could play a role in the later stages of thrombosis.

The two Journal of Biological Chemistry (JBC) Classics reprinted here detail some of Nemerson’s studies on factors IX and VII. In the first Classic, Nemerson and Margalit Zur look at the kinetics of the activation of bovine factor IX by factor VIIₐ. Factor IXₐ is involved in the intrinsic activation system (involving plasma factors only) and activates factor X in the presence of factor VIII, phospholipids, and calcium. Factor IX also can be activated by factor VII in the extrinsic pathway. Nemerson and Zur assayed the activation of factor IX using a technique they previously employed for studying the activation of factor X (1) that follows the release of the activation peptide, which has been radiolabeled on the zymogen. They found that the steady state kinetic parameters for factor IX activation depended on tissue factor concentration and that inhibitory effects exerted by high tissue factor concentrations are related to the lipid content of the preparation. Thus, they concluded that “the concentration of tissue factor regulates the ratio of the activation rates of factor IX and factor X at their respective plasma concentrations.”

In the second Classic, Nemerson and his colleagues look at whether or not factor VII can initiate coagulation without undergoing proteolysis. They hypothesized that if the proteolytically active species is a complex of tissue factor and enzyme, then an active zymogen also should bind the cofactor. The scientists found that factor VII inhibits the activation of labeled factor IX by factor VIIₐ when tissue factor is limiting, indicating that enzyme and zymogen compete for the cofactor, and that factor VII does possess intrinsic activity prior to proteolytic activation.

In recognition of his contributions to science, Nemerson received many honors throughout his career. These include the William Dameshek Prize from the American Society of Hematology in 1977, the Wright-Schulte Memorial Lecture in 1989, and International Society on Thrombosis and Haemostasis’ most prestigious award, the Robert P. Grant Medal in 2003. Nemerson was elected to the American Society for Clinical Investigation and the Association of American Physicians and served as the president of the International Society on Thrombosis and Haemostasis.

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REFERENCES


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