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Mergenhagen S E, Snyderman R, Gewurz H & Shin H S. Significance of complement to the mechanism of action of endotoxin. *Curr. Topics Microbiol. Immunol.* 50:37-77, 1969.

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This paper reviews data related to the role of complement in endotoxin action. Newer information on alternative pathways of complement activation as well as on the biologically active cleavage products of complement are discussed in terms of their relationship to the pathophysiology of endotoxin-induced inflammatory reactions. [The *SCI*® indicates that this paper has been cited in over 120 publications since 1969]

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"In the late 1960s, two young physicians, Henry Gewurz and Ralph Snyderman, joined my laboratory at the National Institute of Dental Research as research associates in the US Public Health Service. Gewurz had significant training in immunology and considerable expertise in complement research because of his prior associations with Robert A. Good and Manfred Mayer. Snyderman, fresh out of an internship and residency program at Duke University, expressed an interest in investigating fundamental aspects of the inflammatory response and, more specifically, in studying the role of complement in leukocyte locomotion (chemotaxis). Because of a long-standing involvement in research on bacterial endotoxin, I was particularly interested in learning how inflammatory cells migrate into and become activated in inflammatory foci induced with gram-negative bacteria or their endotoxic lipopolysaccharide. In one of his first experiments, Snyderman showed that lipopolysaccharide, unlike other bacterial products, was not directly chemotactic for polymorphonuclear leukocytes when evaluated *in vitro* in a modified Boyden chamber. However, he found that a low molecular weight (15,000) chemotactic factor could be generated in serum by lipopolysaccharide. This factor could not be produced in heated (56°C for 30') serum or in serum deficient in the fifth component of complement. Earlier work by Peter Ward suggested that complement participated in the production of chemotactic activity; our data indicated that a cleavage product of C5 might be the chemoattractant. Further collaboration with Hyun Shin at Johns Hopkins University and Joerg Jensen at the University of Miami demonstrated conclusively that lipopolysaccharide, as well as antigen-antibody complexes, generated a low molecular weight chemotactically active peptide (C5a) from the fifth component of complement. From that point on, we studied various biological activities generated by the interaction of endotoxins with the complement system which included alterations in vascular permeability, smooth muscle reactivity, and mast cell and platelet degranulation. Many of these activities were mediated by the release of C5a or by other complement cleavage products, and their formation could explain certain of the inflammatory consequences which follow after an injection of endotoxin into a susceptible host. Indeed, C5a has proven to play a central role in mediating inflammation associated with complement activation in a number of human diseases.

"In searching the literature it became evident that others had suggested a role for complement in endotoxicity.[1] Lipopolysaccharides, like antigen-antibody complexes, were efficient activators of the complement system and many of the sequellae of immune complexes *in vivo* could be reproduced with endotoxin.[2] However, similar to the earlier observation of Louis Pillemer,[3] Gewurz showed that lipopolysaccharides, unlike immune complexes, consume each of the terminal components of complement (C3-C9) with minimal, if any, consumption of C1, C4, or C2. These findings, as well as the observation showing preferential consumption of late complement components by cobra venom factor, prompted us to suggest an alternative pathway for complement activation. Our notions became more of a reality when Ann Sandberg and Abraham Osier showed that guinea pig y1 antibodies activated the late complement components with sparing of the earlier components.[4] The availability of guinea pigs lacking detectable C4 provided further evidence for an alternative pathway.[5] The purification and characterization of distinct serum proteins participating in the alternative pathway were provided by extensive studies from several laboratories.[6]

"The value of the review article published in 1969 and the reason that it has been frequently cited are twofold. First, it pointed to complement and its fragmentation products, such as C5a, as potential effectors of the endotoxin shock syndrome. Secondly, it stimulated others to provide precise experimental evidence for the existence of an alternative pathway of complement activation."

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