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Activation of the Alternative Complement Pathway by a Streptococcal Lipoteichoic Acid

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A glycerol lipoteichoic acid antigen from *Streptococcus pyogenes* 1-RP41 was found by rabbit erythrocyte hemolytic assay to activate the alternative complement pathway in human sera. Over a narrow concentration range of the teichoic acid, complement consumption was dose dependent, whereas at higher concentrations of the acid complement consumption could not be detected.

The lipid-associated glycerol teichoic acid (LTA) from the group A streptococcus 1-RP41 has been shown to inhibit the anti-sheep erythrocyte antibody response and enhance the *Escherichia coli* anti-lipopolysaccharide response in mice (3) and to stimulate the phagocytic activity of mouse peritoneal cells (4). Moreover, LTA has been implicated in an allergic haptenic hypersensitivity (1), the induction of immune complex nephropathy (Fiedel and Jackson, submitted for publication), and the formation of renal calculi in rabbits (6). In the course of studies to assess the capacity of counterion complexes to activate the complement system in a manner analogous to antigen-antibody complexes (2), it was observed that counterion complexes between LTA and the polycation protamine (PC) resulted in the consumption of whole complement (CH_{50}) activity in human serum (Fig. 1). Consumption was characterized by a biphasic distribution, with maxima occurring at ratios of PC to LTA of both 20:0.63 and 20:20 (wt/wt, in micrograms). PC alone was not anticomplementary; however, LTA alone over a narrow dose range appeared anticomplementary, with such activity entirely coincident with the first phase of complement consumption observed with the PC-LTA mixtures.

In view of a recent report that teichoic acid obtained from an unencapsulated pneumococcus, strain R36A, may activate the alternative complement pathway in guinea pig sera (7), attempts were made to assess such a possibility for LTA in the human system by using the rabbit erythrocyte alternative pathway hemolytic assay as described by Platts-Mills and Ishizaka (5); the results are presented in Fig. 2. The incubation of LTA in human serum followed by CH_{50} and alternative pathway consumption analyses revealed that over an identical dose range LTA diminished both the CH_{50} values and hemolysis observed in the rabbit assay. These data therefore suggested that LTA from *Streptococcus pyogenes* 1-RP41 could activate and/or interfere with the utilization of the alternative complement pathway to an extent that would be

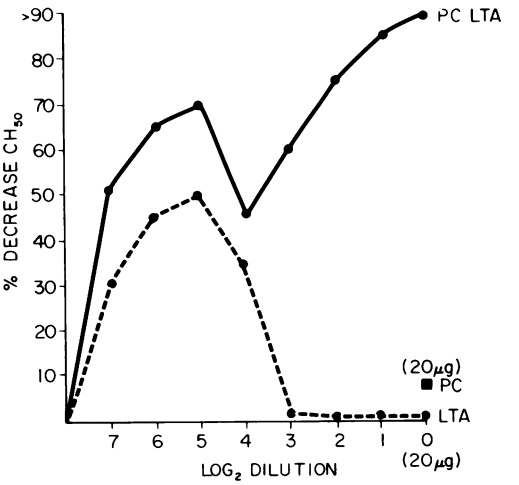

FIG. 1. *Effect of LTA, PC, and PC-LTA complexes upon CH_{50} in human serum. Preparation and characterization of LTA were performed as described previously (1, 3, 4, 6). Buffers, preincubation conditions, and CH_{50} assays were prepared and performed also as described previously (2); PC was obtained commercially. PC was used at a concentration of 20 μg/assay. The greatest concentration of LTA utilized was also 20 μg/assay; lesser amounts of LTA were obtained by serial twofold dilution, as depicted. The data are presented as the average value of triplicate runs (with an internal variation of <8%) and are typical of those obtained in eight individual experiments in which the external variation in the averaged data generated for each point was <10%.*

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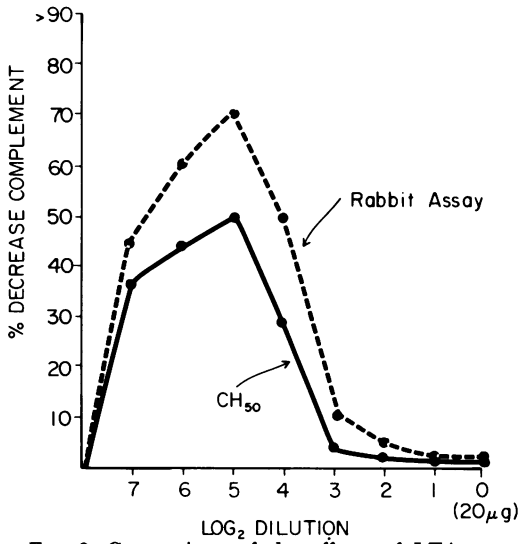

FIG. 2. *Comparison of the effects of LTA upon CH_{50} and alternative pathway consumption in human serum. Alternative pathway consumption was determined by using the rabbit erythocyte assay as described previously (5). The data are presented as the average value of duplicate runs (with an internal variation of <10%) and are typical of those obtained in five individual experiments in which the external variation in the averaged data generated for each point was <10%.*

detectable by CH_{50} analysis, and further, that such an event occurs only over a narrow range of concentrations. The mechanism(s) by which LTA activates or interferes with the activation of the alternative pathway and by which the PC-LTA complexes are functional remains unknown. Nonetheless, these data strongly suggest that LTA, which is freely exuded by the bacterium during the growth cycle, may play an important role in eliciting the host defense mechanism during certain bacterial infections.

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