

Acta haemat. 1958;20:275-276

**An Alternative Hypothesis for the “Properdin System”**

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Experimental results have been obtained which support a hypothesis that the chief characteristics of the “properdin system” may be explained in terms of a classical antigen-antibody system involving complement (C), provided that antibody (Ab) is present in small amounts. Specifically, the hypothesis states that: 1. The zymosan-properdin (Z·P) complex represents varying proportions of Z·Ab·C'<sup>14</sup>, Z·Ab·C'<sup>142</sup> and Z·Ab·C<sup>142</sup> in a decayed state (the amounts of the latter will be dependent upon time and temperature involved in preparation and purification). 2. The purported selective inactivation of C'<sup>3</sup> by zymosan reacting with whole serum was misconstrued from expression of residual C in percentage rather than in units. Since there are 15 to 20 times as many C<sup>4</sup> units as G'<sup>3</sup> units in whole serum, an equivalent loss of both C'<sup>14</sup> and C'<sup>3</sup> units appears to be more significant for C<sup>3</sup> when results are expressed as percentage loss. The presence of Ab in normal serum which reacts with zymosan has been implicated by agglutination, immune-adherence, and complement-fixation. Quantitative uptake of protein nitrogen (N) by zymosan reacting with human sera demonstrated absorbed protein ranging from 1 or 2 µg to 30 or 40 µg N per ml of serum. In quantitative measurements of fixation of G'<sup>14</sup> and of C'<sup>3</sup> (modelled after the procedures of Levine and Mayer) significant amounts of both C'<sup>1</sup> > 4 (about 500 units) and C'<sup>3</sup> (about 150 units) were fixed by zymosan mixed with normal guinea pig serum. Essentially similar ratios of C' components were fixed in assays with *Diplococcus pneumoniae* and bovine serum albumin mixed with small amounts of their respective antibody. These results suggested that certain unique aspects of the properdin system could be explained as due to the small amount of Ab available in normal serum.

Another presumably unique aspect of the properdin system involves: a) the requirement for Mg<sup>++</sup> both in the formation of Z·P and in the reaction of Z·P with C'<sup>3</sup>; and b) the requirement for concentration of Mg<sup>++</sup> which are about 10 times the optimal for lysis in the classic hemolytic system. Independent studies

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by Woodworth demonstrated that optimal reactivity of human C in immune-adherence assays requires .01 M Mg<sup>++</sup> and .001 M Ca<sup>++</sup>, both of which are strikingly higher than needed in immune hemolysis with guinea pig serum. Also, evidence has been obtained which shows that the complex Z·Ab·C'<sup>1</sup> > 4 > 2 may be formed and that this complex reacts with C<sup>3</sup> in the absence of either Ca<sup>++</sup> or Mg<sup>++</sup>. On the basis of the work of Levine and Mayer it would be expected that decay of this intermediate would require Mg<sup>++</sup> in order to fix new C'<sup>2</sup> before reacting with C'<sup>3</sup>.

In the presence of a chelating agent and at 0°C, purified properdin, obtained from Dr. L. Pillemer, agglutinated zymosan. Under the same conditions, initial measurements of N uptake by zymosan indicate that about 0.25 µg protein N are contributed by amounts stated to be equivalent

to 1 unit of properdin. Addition of purified properdin to mixtures of zymosan with guinea pig or with human serum results in significantly greater fixation of C'1 > 4 than in controls with zymosan and serum only.

These results are interpreted to mean that the basic factors involved in the properdin phenomena are natural Ab reacting with C. As yet little information is available on the origin and specificity of the Ab. Since the majority of antigens currently employed in the properdin assays are polysaccharides or lipo-poly-saccharides it would seem reasonable to assume that the supposed broad spectrum of activity is a reflection of the wide distribution of the antigen, perhaps analogous to the distribution of Forssman antigen, Wassermann antigen, or certain polysaccharides common to Salmonella, rather than to a unique nonspecificity of the antibody.

#### Discussion

G. F. Springer (Philadelphia): I do not think that the interesting slide from Pillemer and Wurtz, which was shown to us by Dr. Wedgwood, contains data which might be used for an argument against Dr. Nelson's hypothesis. That some of this dextran does not fix complement while taking up properdin, has its analogy in the blood group field, where purified A and B blood group substances do not fix complement, while reacting with their respective antibodies.