Phospholipid Binding Antibodies Warrant Continued Investigation

To the Editor:

In his excellent review of antibodies to lipids and lipid membranes, Carl Alving discussed how difficult it was for early immunologists to accept the existence of 'anti-lipid' antibodies. This is no less true today and many doubt the existence of antibodies specific for phospholipids and the possibility that they play a role in disease pathogenesis. Hence, Roubey's recent review in Blood is one of a growing number of commentaries that argue that 'antiphospholipid antibodies' present in the 'antiphospholipid syndrome' (APS) are a 'heterogeneous' family of antibodies specific for a variety of plasma proteins such as \( \beta_2 \) glycoprotein 1, prothrombin, or protein C. Although we recognize that there are good data supporting the presence of such antibodies in some patient groups, there remains a considerable and growing body of data that show that phospholipid binding antibodies do occur in the APS and may themselves be pathogenic.

Phospholipids play an important role in the lupus anticoagulant (LA) test.\(^7,8\) The sensitivity of the LA test varies inversely with concentration of phospholipids present in plasma.\(^9,10\) These observations,\(^11,12\) as well as the association of the LA test with biologic false-positive tests for syphilis, stimulated investigators to devise the first anticardiolipin test.\(^13\) In both the original, relatively crude cardiolipin assay devised in 1983\(^14\) and with updated assays,\(^15\) the majority of LA-positive plasma samples yield positive antiphospholipid tests. Both antiphospholipid antibodies and antibodies with LA activity have been simultaneously absorbed by negatively charged phospholipids from plasma\(^16\) and plasma-free systems.\(^17\) Affinity-purified cardiolipin antibodies from patients with the APS have been shown to inhibit prothrombin-thrombin conversion in a system free of \( \beta_2 \) glycoprotein 1, and this inhibitory activity was neutralized by increasing concentrations of phospholipids.\(^18\) Annexin V (placental anticoagulant protein 1), a protein that binds negatively charged phospholipids, has been shown to inhibit cardiolipin binding activity of antiphospholipid antibodies,\(^19,20\) prolong the LA test,\(^21\) and antagonize the prothrombinase inhibitory activity of purified antiphospholipid antibodies.\(^22\) The latter effects are best explained by Annexin competing with antiphospholipid antibodies for phospholipid epitopes both in the cardiolipin test and in the coagulation system.\(^23,24\)

There is also growing evidence to support a direct role of antiphospholipid antibodies in disease pathogenesis. In particular, there are a number of recent studies that have shown that passive immunization of pregnant mice with polyclonal\(^25-27\) or monoclonal\(^28\) antiphospholipid antibodies caused fetal resorption\(^29,30\) or fetal death\(^31\) in the recipients. In addition, one group has shown that antibodies isolated from patients with the APS-enhanced thrombus formation in a murine model,\(^32,33\) and an unpublished study (Pierangeli et al) suggests that antiphospholipid antibodies are responsible for these effects.

Modern immunology has dealt primarily with antibodies specific for protein antigens; perhaps for this reason, interest in phospholipid binding antibodies has often been peripheral. Recent publications suggesting that these antibodies bind proteins or proteins complexed to phospholipids are more in keeping with classical views about autoantibodies and have therefore engendered great interest and speculation that protein binding properties are central to the pathophysiology of the APS. However, evidence supporting the existence of antiphospholipid antibodies and their possible role in the APS cannot be dismissed and warrants further study.\(^34\)

From a purely clinical perspective, we are concerned that hypotheses based on studies of relatively small numbers of plasma or serum samples may disrupt the careful efforts made in the laboratory and clinic to identify patients with the APS. It is not unimaginable that individuals may soon be promoting enzyme-linked immunosorbent assays and other assays for autoantibodies to a bewildering variety of plasma and other proteins, any and all purportedly present in the APS. It was to avoid just this confusion that the Kingston Antiphospholipid Study Group was established and was charged with the responsibility of standardizing the cardiolipin and LA tests used to diagnose the APS.\(^35\) These efforts have yielded relatively well-defined patient cohorts with the APS\(^36,37,38\) and enabled us to obtain useful information about prognosis and management. The loss of this consensus promises confusion for the practicing clinician with respect to diagnosis of the APS and will ultimately do these patients a disservice.

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