46 The Future of Hughes Syndrome

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Five years ago, in these pages, at the request of the editors, I speculated about the future of the antiphospholipid antibody (aPL) field. I argued for more precise clinical distinctions and for answers to several explicit biological questions and noted the absence of the large-scale clinical collaborations that are necessary for clinical studies to advance. Progress since then has been considerable. Table 46.1 lists the questions I raised in 2000 and compares them to the answers available in mid-2004.

What a remarkable period it has been! Many of the old questions have been answered and much new information has accrued. Major contributions have come from Asia and Europe, from the Middle East and Africa, from Australia and all the Americas. Consensus statements from the 10th International Antiphospholipid Antibody meeting in Taormina helped standardize vocabularies, clinical approaches, priorities, and more consensus documents will come from the meeting in Sydney in late 2004. Investigators in the Hughes syndrome field have learned to analyze separately, in treatment and prognosis studies, patients with arterial thromboses from those with venous thromboses or with pregnancy loss only. Most clinical

Table 46.1. Desires for the Hughes Syndrome field in 2000 and status of those desires in 2004. Those items indicated by asterisk are less close to resolution.

2000 questions	2004 status
Clinical distinctions to make	
Hughes syndrome vs. non-immunological coagulopathies	Distinct but similar causes of thrombosis are now understood
Patients with pregnancy loss vs. venous vs. arterial thrombosis	Need for separate patient groups for treatment and outcome studies now understood, but not enacted
Onset of antibody vs. onset of clinical illness	Antibody known to be present 10+ years before syndrome
Causes of thrombosis	*Trigger causes suspect, none identified
Biological questions	
Specifics of antigen and antibody	*Greater detail known, no defined pathogenesis as yet
Mechanisms of coagulation	*Greater detail known, no defined pathogenesis as yet
Mechanisms of valvulopathy, nephropathy, livedo	*Not understood
New animal models	Additional model available, more information on current models
Interpretation of discordant aCL/LAC/β_2-GP1	*Not understood
Needs	
Establishment of consortia for clinical trials	APSCORE, EuroPhospholipid Consortium, others
Clean descriptions of outcomes	Prospective studies underway

studies now carefully distinguish between patients with the primary and those with the secondary form of the syndrome. The distinctions are critical for prospective studies, especially those on treatment. Prospective studies that actually make these distinctions, however, have only just begun; definitive answers will not be available for another few years.

Thrombosis is the defining feature of Hughes syndrome. Simple thrombosis does not explain many of the syndrome's aspects, however, and it is possible that anticoagulation will prove to be an incomplete, insufficient treatment for many of its symptoms. Statins may have a therapeutic role for reasons related to their effects on endothelium or inflammatory mechanisms. We do not yet understand the pathogenesis of, and cannot assume the effectiveness of anticoagulation for livedo, valvulopathy, cognitive dysfunction (with or without hyperintense brain lesions on magnetic resonance imaging), or renal thrombotic microangiopathy. The reasons for the sudden occurrence of the catastrophic antiphospholipid syndrome (CAPS) remain a mystery, as do those for pulmonary hemorrhage. We now know that aPL arises years if not decades before clinical illness, a fact that encourages us to maintain clear distinctions between etiological agents and triggers of clinical events and between aPL and Hughes syndrome itself. How the separate parts of the concatenation of illness – genetic susceptibility, antibody acquisition, first clinical event, and long-term complications – relate to one another is unclear. We are now more aware of surgical risk and of risk of losing renal transplants to thrombosis despite prophylaxis. Systematic cross-sectional studies may have excluded one hypothesis prevalent in 2000, that aPL induces accelerated atherosclerosis; other clinical correlations remain true. Very simple facts – What is the risk in a given circumstance for a new thrombosis? What are the effects of contributing factors, such as smoking, oral contraceptive treatment, or surgery on thrombosis risk? – remain to be defined.

The basic science of this field has also advanced rapidly but has yet to yield definitive answers. We now know a great deal about the binding properties of aPL; its avidity and valence; the peptide and tertiary structure of and the effect of directed point mutations and deletions on β_2-glycoprotein I; the relationships between aPL and antibodies to other phospholipid binding proteins, such as prothrombin; and the roles in the syndrome of plasmin, tissue factor pathway inhibitor, and other effectors or markers of thrombosis and fibrinolysis. New animal models for thrombosis, knock-outs and mutated animals, and animal models for neurologic disease assist us to understand pathogenesis. Animal mutations and modulations demonstrate a requirement for complement activation in experimental pregnancy loss. Animal preparations that monitor in vivo adhesion of cells or cell particles in flowing blood may serve as tests of treatment efficacy. In humans, the roles of endothelial cell and platelet activation in clinical events have been studied in detail. Studies on microbial peptides that cross-react with β_2-glycoprotein I suggest etiologies and potential treatments. But, oddly, compared to other (rheumatic) illnesses, the science of Hughes syndrome has accrued less information about its genetics, potential roles (if any) of cytokines, functions or abnormalities of specific immunocytes, cell surface markers, and cell activation cycles. Is this because thrombosis is thought not to be immunologic or because Hughes syndrome is not thought to be a systemic autoimmune disease? Or is it that, absent evident immune attack, these sciences do not apply?

Despite thousands of papers, the clinical needs of this field remain great. Standardization of clinical definitions among studies is an absolute requirement, a