Hughes Syndrome
To my daughter Leila
I am very happy to be asked by Dr. Munther Khamashta to write a Foreword to this first comprehensive description of the many facets of the antiphospholipid syndrome (APS). Although I have been an interested and long-time participant in studies to elucidate the nature of some human diseases associated with immunological abnormalities, I have not had a personal involvement with work on the APS. I have however watched with great fascination the evolution of this field from initial observations of clinical symptoms to studies defining the pathophysiological abnormalities.

The APS began with reports in 1983, 1984 and 1985 (see Khamashta: Hughes Syndrome, A History) on a number of clinical symptoms which appeared to have an underlying common pathogenic mechanism – vascular thrombotic episodes. These included peripheral vascular thromboses, cerebral vascular infarctions, livedo reticularis, spontaneous abortions and portal and pulmonary hypertension. A striking feature of this unfolding story was that already in 1983, suspicion was cast on the likely association of anti-cardiolipin/phospholipid antibodies with the clinical syndromes. Continuing studies on the pathophysiology have helped to fine-tune the immunological abnormalities. Most investigators believe that proteins complexed to phospholipids such as β-2-glycoprotein-1 are the primary targets of the autoantibodies but there appears to be continuing evidence that phospholipids themselves are also target antigens. The argument here may hinge on the fact that the immunogen itself might be a complex of phospholipid and protein and the humoral immune response is directed at different component parts of this complex, depending on the “immunogenicity” of different components to a genetically susceptible host. In fact, many autoantigens in lupus and other autoimmune diseases are complexes of nucleic acids and proteins, a classical example being the Sm antigens comprising complexes of small nuclear RNAs and small nuclear ribonucleoproteins.

In autoimmune diseases like lupus, we have advanced the notion that the humoral antibody responses are antigen-driven and that the antigens are self proteins rendered immunogenic due to a variety of reasons, including overexpression, ectopic localization and structural alterations of various kinds such as mutagenesis or complexing with foreign materials. An interesting aspect of the APS story is the diverse nature of clinical symptoms which involve totally different organ systems but rarely involve more than one organ system at a time. This is in contrast to lupus which is also a multi-system disease, but the individual patient often has multiple organ
system involvement. It is possible that the APS might fall into the following mechanistic scenario:

**Different inciting agents → → → Thrombosis in different organ systems → → → antigenic modification of procoagulant phospholipid-protein → → → humoral antibody responses → → → in-situ antigen-antibody complex formation → → → inflammation, further thrombosis, recruitment of cellular immune infiltrates → → → perpetuation of repeated cycles of thrombosis, inflammation and immune responses.**

The diversity of the APS could be explained on the uniqueness of the initial inciting event leading to pro-coagulation occurring in specific organ systems and thus would not have to invoke aberrant immune responses manifesting the great variety of clinical syndromes. One of the challenges in the future would be to explain or identify the different inciting agents for the different syndromes encountered.

One of the issues which has been raised is that the anti-phospholipid syndrome is a misnomer since the major target antigen appears to be the protein or the lipoprotein complex. Many investigators are inclined towards keeping the original moniker of the APS because of both historical and common usage reasons. The history of clinical medicine and biomedical research is replete with examples where original designations have been retained in spite of subsequent studies showing that the designation was not totally correct. The important thing is that the essence of the original observations in the APS was correct.

It is rare that an investigator and his colleagues have the opportunity to open up a new field in clinical medicine and biomedical research. This has happened with the anti-phospholipid syndrome. Graham Hughes and his colleagues deserve enormous kudos for recognizing that a number of clinical syndromes shared a common feature of vascular thrombosis and for carrying this into consolidation of the clinical observations with laboratory analysis. Much clinical and basic research by many investigators worldwide have resulted from these beginnings. This volume stands as a tribute to Hughes and his colleagues.

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Memory loss, migraine, strokes, accelerated atheroma, recurrent miscarriages – some of the features which make the antiphospholipid syndrome (APS) so important to patients and clinicians worldwide.

The finding that simple and reproducible assays can identify patients at risk both for venous and arterial thrombosis has opened up new avenues for treatment across many specialties.

From the early days in the late 1970s and early 1980s, I had felt strongly that the syndrome would one day outstrip lupus in frequency. Indeed my colleagues and I were often impatient at the seemingly slow acceptance of the syndrome by the medical (and obstetric) community in the early years. All that has changed. The number of papers and meetings relating to the syndrome has become a flood, and there is widespread realisation that this may, in fact be one of the most common and important auto-immune diseases.

My grateful thanks to my colleagues, mentors and friends, especially Dr Tan and Charles Christian, whose guidance I have always valued, and to Nigel Harris and Aziz Gharavi, who not only worked with me in the early days of the syndrome, but have become world leaders in APS research.

Most of all, my grateful thanks to Munther Khamashta, my colleague and friend for a decade.

His reputation in this field is truly international. It is a testimony to his personal qualities that he has been able to persuade the world leaders in APS to contribute to this volume.

Graham Hughes
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