1 Hughes Syndrome: History

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In the 21 years since Graham Hughes's detailed description of the antiphospholipid syndrome (APS), the condition has come to be regarded as one of the most common autoimmune diseases. The impact of the description has been enormous – for example, the recognition that some individuals with connective tissue diseases require anticoagulation rather than steroids or anti-inflammatory treatment has brought about a fundamental change in medical practice. In obstetrics, APS is now regarded as the most important prothrombotic cause of recurrent pregnancy loss – with pregnancy success improving from below 20% to a current live birth rate of over 80% [1].

In neurology, Hughes syndrome may be associated with up to 20% of strokes in people under 40 – a striking figure not least in terms of medical economics, let alone in potentially preventable suffering.

In vascular disease, Hughes syndrome may well provide insights into immunological factors in the pathogenesis of atheroma [2].

In short, the syndrome links immunology with thrombosis and vascular disease. The mechanisms are complex and our current knowledge will be detailed in this volume. Suffice to say that the antibodies probably bind not simply to phospholipids – nor simply to phospholipid cofactor. In view of this increasing complexity, colleagues at the Sixth APS meeting in Louvain put forward the eponym *Hughes syndrome* in honor of the physician who fully described the condition – an eponym with which most colleagues working in the field, and those contributing to this volume, are content.

Graham Hughes's description of the condition was not, as is sometimes the case, based on a single case report or a small series. It was a truly comprehensive and lifetime work, starting in the world of lupus. The 1983 description of the syndrome was the culmination of a decade of work in which careful clinical observations were combined not only with scientific studies, but also with a sharing of information. His ward rounds were and are famous for the cross-fertilization of ideas.

In 1983–1986, Dr Hughes and his team described the association of antiphospholipid antibodies (aPL) with *arterial* as well as venous thrombosis; with neurological disease, especially stroke; with pulmonary hypertension; with livedo; with occasional thrombocytopenia; and with recurrent miscarriages. More significantly, he recognized that this syndrome, which he initially named the anticardiolipin syndrome and later the primary antiphospholipid syndrome, was separable from lupus. My colleague, the late Aziz Gharavi, remembered hearing Graham forecast, at the 1985 American College of Rheumatology meeting in New Orleans, that the

"primary" APS would one day outstrip lupus in prevalence, and that in the world of obstetrics, anticoagulation would replace steroids in the management of recurrent fetal loss in this disease. Both forecasts are proving correct. In the early 1980s Graham Hughes's team, led initially by Drs Nigel Harris and Aziz Gharavi, and later by myself, instituted collaborative workshops and, in 1984, the first international APS meeting – a meeting which has become a regular fixture and which spawned the classification criteria [3, 4]. The following extract is, with permission, taken from Dr Hughes's own account of the description of the APS [5]:

> The description of the syndrome in 1983 came after a number of years of study of lupus, of myelopathy (especially so-called Jamaican neuropathy) and of atypical forms of connective tissue disease. We had become interested in the association of a false-positive VDRL with transverse myelopathy, and hypothesized, probably wrongly, that anticardiolipin antibodies might cross-react with neuronal phospholipids including cephalin and sphingomyelin [6]. With our large clinic population, it is relatively easy to spot subsets of disease and it soon became apparent that the presence of anticardiolipin antibodies (also the lupus anticoagulant) – hence antiphospholipid antibodies, were strongly associated with thrombosis and miscarriage. From a clinical point of view, the association with thrombosis related not merely to venous thrombosis, but – differentiating it from almost all other prothrombotic conditions – *arterial* thrombosis, especially strokes.
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> In 1983, I was invited to present my findings to a British dermatology society meeting – the "Prosser White oration" [7]. The following extract, taken from that paper, highlights, I believe both the clinical features of the syndrome, and the recognition of a "Primary" antiphospholipid syndrome:
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> Although many of these patients fall under the general heading of lupus, or lupus-like disease, I believe that the group is sufficiently homogeneous, and in some ways (such as the frequently negative ANA serology) sufficiently different from typical systemic lupus erythematosus (SLE) to warrant separate consideration. The manifestations of this syndrome are thrombosis (often multiple) and, frequently, spontaneous abortions (often multiple), neurological disease, thrombocytopenia and livedo reticularis. The livedo reticularis is often most florid on the knees. This may or may not be associated with mild to moderate Raynaud's phenomenon.
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> These patients' blood pressure often fluctuates, apparently correlating with the severity of the livedo, suggesting a possible renovascular aetiology. However, this group of patients rarely has primary renal disease.
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> The cerebral features are prominent and of three varieties: headaches – often migrainous and intractable; epilepsy (or abnormal EEGs) – often going back to early teenage. Fortunately, severe or difficult-to-control epilepsy is infrequent. Some patients have chorea. Cerebro-vascular accidents – sometimes transient and seemingly attributable to migraine, are frequently progressive.… The patients may develop transient cerebral ischaemic attacks or visual field defects, or, more significantly, progressive cerebral ischaemia.
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> Two other features of the syndrome are a tendency to multiple spontaneous abortions and peripheral thrombosis, often with multiple leg and arm vein thrombosis. We have also seen Budd–Chiari syndrome and renal vein thrombosis in some of these patients. We have, of course, tended to group these patients under the diagnostic umbrella of systemic lupus, though an alternative label of "primary" Sjögren's syndrome covers other patients, and characteristic dry Schirmer's tests and lymphocytic infiltration of the minor salivary glands have been found in a number (though not all) of this group of patients.
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> To my mind, however, the most striking, and often the most serious feature of the disease is the tendency to thrombosis, particularly cerebral thrombosis. So prominent has this feature been that we have some patients in their 40s and 50s who had been diagnosed as primary cerebrovascular disease or – when the labile hypertension has been observed – as hypertensive cerebrovascular disease. The finding that many of these patients may have