Hughes Syndrome — the Syndrome behind the Name (otherwise known as Antiphospholipid Syndrome)

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It is a privilege for me to be asked to write a short article on the history of the antiphospholipid (Hughes) syndrome for the Israel Medical Association Journal. From the early days of our description of the prothrombotic syndrome in 1983 [1,2], our research links with the group of Yehuda Shoenfeld have been hugely productive [3].

The description of the syndrome in 1983 came after a number of years of studying lupus, myelopathy (especially the so-called Jamaican neuropathy), and atypical forms of connective tissue disease. We had become interested in the association of a false-positive VDRL test with transverse myelopathy, and hypothesized, probably wrongly, that anticardiolipin antibodies might cross-react with neuronal phospholipids including cephalin and sphingomyelin [4].

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.

In 1983, I was invited to give the "Prosser-White Oration" at a British dermatology society meeting, which was an opportunity for me to present my findings [2]. 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:

> 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 A.N.A. 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 reno-vascular 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. Cerebrovascular 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.
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> We have, of course, tended to group these patients under the diagnostic umbrella of systemic lupus, though an alternative label of 'primary' Sjogren'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. 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 high titres of circulating anti-cardiolipin antibodies leads us to believe that a new line of investigation may be possible in such patients.

In 1994, colleagues at the Sixth International Antiphospholipid Conference in Louvain honored me by calling the syndrome "Hughes Syndrome." This accolade brings me

great pleasure. I genuinely feel that this eponym, unlike some others in medical history, is based on more than a case report or two. Our descriptions of the syndrome, I believe, are comprehensive. In the early eighties my team, then at Hammersmith, collected large numbers of patients who had the syndrome but did not meet the classification criteria for lupus. We called this entity "anticardiolipin syndrome," and changed the name to the "antiphospholipid syndrome" when it became clear that these patients' sera were also cross-reactive with other phospholipids such as phospatidyl serine [5–7].

So, in the few years between 1983 and 1987, our description of the syndrome included recurrent fetal loss [8], livedo [2], renal thrombosis [9], stroke [10], myelopathy [11], chorea [12], bowel infarction [13], thrombocytopenia [14], pulmonary hypertension [15,16], and dementia [17].

The clinical collaborators included Margaret Byron, Bernie Colaco, Genevieve Derue and Mee-Ling Boey, who were later joined by Charles Mackworth-Young, Sozos Loizou, Bupendra Patel, John Chan, Keith Elkon, Mark Walport and Ron Asherson. In the laboratory, two research fellows — Aziz Gharavi and later Nigel Harris — spearheaded the development of immunoassays culminating in the first paper (published in *The Lancet*) on the assay for anticardiolipin antibodies [18], which paved the way for the development of the enzyme-linked immunosorbent assay [19] and the widespread testing and recognition of the syndrome. (For those who feel discouraged by rejections, take note, it took two years for *The Lancet* paper to be finally accepted, all Nigel Harris's early grant applications were rejected, and doubts were raised about his career prospects! He is now a dean of medicine in Atlanta).

Finally, we arranged the first international meetings and workshops on antiphospholipid syndrome — the first in 1984 in Hammersmith, and the second in 1986 at St. Thomas' hospital after our move there [20]. These workshops have been *truly* international; the most recent, in 1998 in Sapporo [21], is leading the way in the consensus on classification criteria for Hughes syndrome. The next, in the year 2000, is to be held in France and is being arranged by my friends Marie-Claire Boffa and Charles Piette.

The Primary APS — Hughes Syndrome

In the 1983 Prosser-White lecture, I emphasized my view that many of the patients did not have classical lupus and deserved separate consideration as representing a syndrome [2]. In the early 1980s we published a number of reports associating antiphospholipid antibodies with the syndrome *outside* of systemic lupus. We reported aPL[1] in Behçets disease, idiopathic transverse myelopathy and Guillain-Barre syndrome [22], idiopathic thrombocytopenia [14], migraine, epilepsy [23], heart valve disease [24] and Addison's disease [25]. In short, lupus itself need not necessarily be present…

> A distinct syndrome it most certainly is. It occurs in ANA-negative LE patients, atypical lupus patients and, as expected, individuals with no lupus at all [5].

In 1987 we first introduced the terms "antiphospholipid syndrome" and "primary antiphospholipid syndrome" [6,7]; and 2 years later, in 1989, two large series of patients were reported — one by our group [26] and another by the group in Mexico [27] — confirming and detailing the earlier clinical descriptions.

The next major advance came in 1990, when three groups [28–30] reported that aPL required a plasma protein "co-factor" to bind cardiolipin on ELISA plates. This co-factor was identified as β_2-glycoprotein I. Since that time, a number of "co-factors" have been described, including prothrombin [31]. The binding of antibodies to the antigen site is clearly complex and dependent on molecule configuration. Our own studies using monoclonals have, for example, suggested binding to a trimolecular site including phospholipid, protein C and co-factor [32]. Thus, even the cumbersome term "phospholipid-co-factor syndrome" is probably wrong.

The Past

Most observers of lupus, from Osler on, have recognized that thrombosis is a feature of some patients. Likewise, many other features of the APS[2], including thrombocytopenia and recurrent miscarriage, are well recognized as features of the disease. The historically "oldest" immunological finding in systemic lupus erythematosus is the Wasserman reaction. Moore and Mohr in 1952 recognized that their false positive (BFP.STS) syphilis tests could occur in lupus [33]. Laurell and Nilsson [34] found that the "lupus inhibitor" was frequently associated with BFP.STS.

In clinical studies of lupus, Bowie et al. [35] reported the occurrence of thrombotic lesions in patients with a circulating anticoagulant. The first report of a patient with lupus anticoagulant and recurrent abortions was by Beaumont in 1954 (36). This was followed by similar observations by Nilsson et al. [37] 20 years later, and another 5 years later by Soulier and Boffa [38]. These, and other similar case reports in lupus patients, do, in retrospect, anecdotally support the long history of the syndrome.

The Future

There are a number of avenues of research — epidemiological, clinical, mechanisms of thrombosis, and the possible role in accelerated vascular disease. The epidemiology (and genetics) are gradually being reported. There may be interesting ethnic differences. Malaviya et al. [39], for example, have reported that Hughes syndrome may be more common in Arab groups than in Indians. There is also an intriguing observation that APS may be less common in blacks than in whites.

[1] aPL = antiphospholipid antibodies

[2] APS = antiphospholipid syndrome

The clinical features continue to accumulate. It is now known that the disease is a *major* cause of stroke — possibly accounting for up to 20% of strokes in the under 45-year olds. The syndrome has also had a major impact on obstetrics, accounting for up to 25% of cases of recurrent miscarriage, and proving that recognition and thus treatment of the condition can vastly improve outcome [40].

As to mechanisms, effects on thrombosis and on the endothelium have been demonstrated, and the development of animal models — notably by Yehuda Shoenfeld and his group, and Aziz Gharavi and Nigel Harris — have added substantially to our knowledge [41].

Finally, one of the most intriguing aspects of the syndrome has been the demonstration of accelerated arterial disease in some APS patients. Outi Vaarala and colleagues first demonstrated possible cross-reactivity between aPL and oxidized low density lipoproteins. This has led to the development of assays for anti-oxLDL and anti-LP(a), to mention two, and their possible association with accelerated atheroma [42]. Thus, "Hughes syndrome — a crossroads of autoimmunity and atherosclerosis" [3] — may provide insights into immunological mechanisms in the development of accelerated atherosclerosis.

The literature on the syndrome is now huge, and the interest in these patients now embraces almost all medical disciplines. In my original article in 1983, I wrote:

> For those of us hardened into nihilism by years of study of various autoantibodies in systemic lupus erythematosus, there is a rare sense of excitement at the implications of the associations now being reported [1].

For me, that excitement is still present.

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