Alarcón-Segovia: Editorial 1893

Throughout the history of humanity, and except for a few contributions by true pioneers, each bit of new knowledge or new development has been based on the work of many others, often unknown, who have helped build the corresponding edifice. Each milestone takes up so many yards, inches, centimeters, or millimeters according to the relative importance of the apparent new knowledge. However, the lack of even an apparently millimetric step, in this same sense, might prevent reaching the milestone. Stephenson may not have thought about it, but his invention of the railroad steam engine was only possible because throughout history people had learned to harness fire, including the unknown primitive humans who first learned to produce and keep it.

I will attempt to recount the saga of the antiphospholipid syndrome (APS), including my own experiences, with the precision of the scientist, the insight of one who has lived through it, and the emotion of one who sees in this story a wonderful example of the sum of contributions made for the sake of knowledge and helping fellow humans. Interest in this topic should not falter if we are to understand it fully, and with this understanding be able to provide our patients with a definitive solution.

I would like to take you as far back as 1906, to Wassermann and his coworkers1, who developed serological reactions for the diagnosis of syphilis utilizing phospholipid-rich tissues as antigens, later to be termed cardiolipin by Pangborn (1941)2. The finding of individuals who were positive for these reactions, but who were either too pious or too young to be suspected of having acquired syphilis, first brought about the possibility of false positive serological reactions for this disease, and tests were developed to distinguish these from the true positive reactions.

The first milestone resulted from the attempt to determine who, and perhaps why, some individuals had such false positive reactions for syphilis, and the finding that the majority were women who, when followed by Moore and Lutz (1955)3 for enough time, developed systemic lupus erythematosus (SLE). Interestingly, 3 of their 21 lupus patients with antecedent false positive tests for syphilis had had major unexplained thrombophlebitis. Here we should acknowledge the contributions, albeit indirect, of Hargraves, Richmond, and Morton (1948)4, who found LE cells that permitted a more ample diagnosis of SLE, and of Edmund Dubois (1953)5, who helped us recognize its wider clinical spectrum.

The second milestone resulted from the search for the cause of bleeding in a patient by Conley and Hartmann (1952)6, with the resulting finding of an inhibitor of coagulation that was subsequently related by Sánchez-Medal and Lisker (1959)7 from our own institute to patients with SLE, most of whom did not bleed.

The paradox encountered by Bowie and his coworkers (1963)8 of a frequent occurrence of thrombosis, rather than bleeding, in patients with SLE who had this inhibitor of coagulation, subsequently termed lupus anticoagulant by Feinstein and Rapaport (1977)9, marks the initiation of the concept of APS, particularly when somewhat later Thiagarajan, et al (1980)10, found that at least some of the lupus anticoagulants actually were antiphospholipid antibodies (aPL).

Shortly after the study of Bowie and his coworkers, and stemming from the same institution, Alarcón-Segovia and Osmundson (1965)11 described 11 patients with SLE who had peripheral vascular syndromes. Some of these are particularly interesting: one had chronic ulcers of the legs and livedo reticularis, clinical manifestations later found to be associated with aPL, and both circulating anticoagulants and false positive serologic tests for syphilis; another patient had had 4 miscarriages, thrombophlebitis, livedo reticularis, thrombosis of the left ulnar artery, convulsions, and long-standing false positive tests for syphilis; a third patient had false positive tests for syphilis, recurrent superficial thrombophlebitis, leg ulcers, intermittent claudication with evidence of popliteal artery occlusion, a vascular lesion of the brain stem, and a terminal occlusion of a basilar artery.


In 1980 Soulier and Boffa14 recorded the occurrence of recurrent abortions, thromboses, and a circulating anticoag-
ulant in patients not having a primary condition, and in 1981 Carreras and his coworkers\textsuperscript{15} studied the possible role of inhibition of prostacyclin formation by the lupus anticoagulant in the causation of thrombosis.

The next milestones in the antiphospholipid story resulted from the development of more sensitive tests for aPL: in 1980 radioimmunoassays by Smolarsky\textsuperscript{16}, by Harris and coworkers in 1983\textsuperscript{17}, and more practical, an ELISA developed by Loizou and his coworkers, using cardiolipin as antigen (1985)\textsuperscript{18}. The more ample use of these tests permitted Hughes\textsuperscript{19} to propose the occurrence of an anticardiolipin syndrome in patients with SLE (1985). In some of his writings at that time Hughes mentioned that there were some patients with this syndrome who had no lupus, but he did not actually describe such patients.

The notion that within SLE there might be patients with a set of manifestations caused by one of their multiple autoantibodies and thus have a specific syndrome seemed interesting enough to me to try to confirm it. I therefore wrote Graham Hughes requesting some specific instructions on their anticardiolipin ELISA. I obtained a prompt response from Nigel Harris with instructions as well as anti-cardiolipin properties and high affinity for anionic molecules such as cardiolipin. Moreover, as noted by Takao Koike, pathogenic antibodies can be distinguished from those present in infectious disease (e.g., syphilis). The pathogenic antibodies require the presence of bovine serum with such cofactor, the infectious antibodies do not, he said. The corresponding articles were published that same year (1990)\textsuperscript{28-30}.

At a \(\beta_2\)-GPI symposium in Milan in 1992, Cabral and his coworkers described the presence of anti-\(\beta_2\)-GPI antibodies in a group of patients with primary APS\textsuperscript{31}; this finding was also published by Viard, et al that year\textsuperscript{32}. That these antibodies may have the most important role in the causation of the APS, particularly its thrombotic component, was evidenced by their systematic fall at the time of thrombosis, as found by Gómez-Pacheco and coworkers\textsuperscript{33} in 1999.

An important study by Matsuura, Koike, and their coworkers\textsuperscript{34} (1995) revealed that the so-called anticardiolipin antibodies could bind to \(\beta_2\)-GPI in the absence of cardiolipin if the ELISA plates were oxidized by irradiation. This procedure was considered by Roubey and coworkers in 1995\textsuperscript{35} to cause higher antigen density and permit bivalent binding. In 1995 Cabiedes, et al\textsuperscript{36} found that manifestations of APS associated more strongly with antibodies to \(\beta_2\)-GPI determined in non-irradiated plates versus those with anti-cardiolipin, and Cabral, myself, and our respective coworkers subsequently (1996, 1997)\textsuperscript{37} described groups of patients with clinical manifestations of APS who had persistently negative anticardiolipin antibodies when studied in conventional assays, but persistently positive anti-\(\beta_2\)-GPI antibodies determined in non-irradiated plates.

In 1988, early in the antiphospholipid story, I began inquiring about the pathogenic potential of aPL in an editorial\textsuperscript{38}, and participated in a series of studies on their role in...
deficiencies of natural anticoagulants, headed by Guillermo and Alejandro Ruiz-Argüelles (1989)39, in a study by Vázquez-Mellado, et al (1994)40 on their role in thrombocytopenia by recognizing \( \beta_2 \)-GPI that had bound to anionic phospholipids switched to the outer leaflet of platelets upon their activation or aggregation, as well as in a study by Cabral, et al41, where we found a role for an IgM natural autoantibody to phosphatidylcholine in the causation of hemolytic anemia (1990).

The synergism between aPL and antiendothelial cell antibodies in the causation of vascular damage in the APS began to be explored by Meroni and coworkers (1992)42, and a potential role of aPL in the causation of atherosclerosis stemmed from the seminal work by Vaarala and coworkers on the crossreactivity between anticardiolipin antibodies with oxidized low density lipoprotein (1993)43.

But perhaps the most important milestone for determining the pathogenicity of antiphospholipid antibodies came with the elegant series of studies by Shoenfeld and his group (1991)44,45, i.e., animal models of the APS induced both by passive and by active immunization, as well as their therapeutic manipulation (1999)46. In addition, these workers identified a hexapeptide that is recognized specifically by pathogenic anti-\( \beta_2 \)-GPI antibodies and by antibodies produced on immunization of mice with microbial preparations. Naïve mice infused with the antipeptide antibodies produced on immunization of mice with microbial preparations. Naïve mice infused with the antipeptide antibody body produced by these immunizations developed clinical preparations. Naïve mice infused with the antipeptide antibody body produced by these immunizations developed clinical evidence of an antiphospholipid syndrome, indicating that molecular mimicry elicited by infections may lead to the development of pathogenic anti-\( \beta_2 \)-GPI antibodies reactive with this peptide (2002)47.

The presence of autoreactive interleukin 6 producing CD4+ T cell clones to \( \beta_2 \)-GPI in patients with APS was recently identified by Kuwana and his group (2001). These cells recognized at least 4 different epitopes, but the majority recognized a 15 amino acid peptide in the phospholipid-binding fifth domain. Most of these T cells stimulated autologous blood B cells to promote anti-\( \beta_2 \)-GPI production in the presence of recombinant \( \beta_2 \)-GPI. In a subsequent study they found that such autoreactive T cells had restricted T cell receptor \( \beta \)-chain usage (VB7 and VB8) (2002)48.

Some of these findings may have implications regarding potential forms of treatment. Other avenues of treatment reside in the induction of tolerance of anti-\( \beta_2 \)-GPI-producing B cells or in anionic blockade of the phospholipid-binding sites of \( \beta_2 \)-GPI by means of heparin or other compounds, as proposed by Guerin and coworkers (2002)49.

Before the concept of an antiphospholipid syndrome originated, lupus patients with venous occlusions and particularly those with arterial occlusions were treated mainly with corticosteroids and immunosuppressives. In addition, patients with primary APS were often diagnosed as lupus and met classification criteria for this disease. This could have been considered reasonable were it not for the unnessary steroid treatment they received instead of merely anticoagulant and/or platelet antiaggregant treatment. We have come a long way in our understanding of the antiphospholipid syndrome. In looking back, I cannot help but feel that the wheels of the antiphospholipid story are turning more slowly, and at times even seem to stop. It might be only natural that the previous large scope of studies would now tend to be reduced. However, many unknowns await our renewed vigor. Only with vigor can we attain a brighter future for our patients.

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REFERENCES
16. Smolarsky MA. A simple radioimmunoassay to determine binding