


SYNDROME OF THE BLACK SWAN

A few years ago, after presenting my first case history of a patient with recurrent venous thrombosis and anticardiolipin (aCL) antibodies, a senior physician in the audience remarked that the whole story of an antibody associated with complications such as thrombosis and fetal loss was like a 'swan'. Following a moment's pause, he added a 'Black Swan'. After puzzling about this remark with a colleague, Dr. Yvette Williams, we decided that we would privately refer to this unusual antibody, with its unusual (presumed) clinical associations, as the 'Syndrome of the Black Swan'. For obvious reasons, we decided that the initials B.S. should not be used in referring to the 'syndrome'. In our minds, as perhaps in the mind of the senior physician, we believed that the whole subject of anticardiolipin antibodies and their clinical associations needed to be approached carefully, but there were sufficient clinical data available to argue that clinical associations, although unusual (like black swans), did exist. The Black Swan has acquired a number of names in the last few years, including the Lupus Anticoagulant, Anticardiolipin or Antiphospholipid Syndrome [1–4]. If one were to accept the word 'syndrome', one must still define exactly what clinical and laboratory features constitute this entity. Anticardiolipin antibodies and, to a lesser extent, lupus anticoagulant activity have been found in a variety of connective-tissue, infectious, drug-induced, malignant, and other disorders. Keane and colleagues in the current issue of this journal found aCL antibodies in 44 of 90 patients with rheumatoid arthritis [5]. Another paper recently reported positive aCL tests in 80% of patients with acute myocardial infarction [6]. It seems unlikely that all these patients, the overwhelming majority of whom may have low, transiently positive aCL tests, will have the syndrome. Since the inception of our work, we have found that patients most subject to thrombosis, fetal loss, and thrombocytopenia had moderate to high aCL levels, usually with the IgG isotype [7]. Subsequent studies continue to confirm this general finding [8]. In order to ensure agreement about what constitutes 'moderate to high' aCL levels, we have prepared standard sera with varying IgG and IgM aCL levels and established units for measurement of aCL antibody levels [9]. Freeze-dried aliquots of these sera have been distributed to over 100 laboratories worldwide, and results have been analysed so far from about 30 laboratories. Most laboratories with valid assays obtained good distinction between these standard samples and it may well be possible to reach some decision about what crudely constitutes high, moderate or low aCL levels. The distinction between low positive and normal will always be controversial [9].

Does a patient without thrombosis, fetal loss, or thrombocytopenia who has moderate to high aCL levels and/or an unequivocally positive lupus anticoagulant test have the syndrome? Until patients with positive tests are followed for long enough, one will not know. Only about 25–33% of patients with the lupus anticoagulant [10, 11] appear to develop thrombosis, although it appears that over 75% of LA positive women will suffer fetal loss [12, 13]. At this time, it would seem wise to include patients in the syndrome or 'group' only if they have both a positive aCL test and at least one of the following clinical features: thrombosis, fetal loss, or thrombocytopenia (Table). Other categories of patients, including those with thrombosis or fetal loss who have low positive aCL tests (particularly if low positive IgM or polyvalent) should be followed carefully, but should prob-
Patients with the antiphospholipid syndrome should have at least one clinical and one serological feature at some time in their disease course. An antiphospholipid test should be positive on at least two occasions, more than 8 weeks apart.

*Lupus anticoagulant should be confirmed by demonstrating inhibition by phospholipids or by freeze-thawed platelets (33106-107).

Table: Proposed Criteria for Antiphospholipid Antibody Syndrome

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombosis</td>
<td>IgG anticardiolipin antibody (&gt;20 GPL units)</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>Positive lupus anticoagulant test*</td>
</tr>
<tr>
<td>Recurrent fetal loss</td>
<td>IgM anticardiolipin antibody (&gt;20 MPL units) and positive LA test</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
</tbody>
</table>

Patients with the antiphospholipid syndrome should have at least one clinical and one serological feature at some time in their disease course. An antiphospholipid test should be positive on at least two occasions, more than 8 weeks apart.

*Lupus anticoagulant should be confirmed by demonstrating inhibition by phospholipids or by freeze-thawed platelets (33106-107).

As interest in this syndrome has grown, it appears to be acquiring more and more features—both clinical and laboratory. Additional features include a variety of neurological complaints (in addition to stroke), livedo reticularis, migraine headaches, splenomegaly, cardiac valvular lesions, Coombs' positive tests, positive antimitochondrial tests, and so the list continues. Since many of the affected patients have some other connective-tissue disorder, one wonders which features belong to which disorder. I believe that acceptance of minimal criteria for the Black Swan grouping (Table) may help us decide what are likely features of this grouping and what are features that can be attributed to another cause, another syndrome, or another group.

There is the question of how best to refer to the Black Swan. I prefer the Antiphospholipid Syndrome. The characteristic that these patients have most in common are antibodies that bind a variety of negatively-charged phospholipids including cardiolipin [15]. Although the antibodies of syphilis also bind cardiolipin, we have found that they bind other phospholipids to a much lesser extent than they do cardiolipin, particularly when cardiolipin is mixed with phosphatidyl choline and cholesterol [15]. Hence, syphilis seems to be associated with the only true anticardiolipin antibodies, and patients with syphilis do not appear to suffer the same complications as those with the so-called antiphospholipid syndrome [16].

A word of warning. Although patients with the antiphospholipid syndrome exist, they (like black swans) are probably not found as frequently as enthusiastic medical personnel might like. Only a small fraction of all patients with thrombosis or fetal loss will have this syndrome, but the numbers are large enough and complications severe enough to justify searching for them.

Wisdom suggests that patients with thrombosis or fetal loss who have low positive aCL tests should be treated with caution, and the aCL test repeated after several weeks to ensure that levels are truly elevated. Repeat tests a few weeks later may be negative.

I believe, too, that patients with moderate to high aCL levels without clinical complications should not be subjected to prophylactic anticoagulant therapy to prevent thrombosis and women should not be subjected to prophylactic steroid therapy during pregnancy without a history of fetal loss.

Like most new and somewhat unusual findings in medicine, antiphospholipid antibodies have been greeted with great scepticism by some physicians and with unbridled enthusiasm by others. My view is that these antibodies may prove at least as interesting as other non-organ-specific autoantibodies in SLE and related connective-tissue disorders. On the other hand, the value of studying antiphospholipid antibodies can easily be lost in a sea of over-interpreted and over-reported laboratory and clinical findings.

E. Nigel Harris
Deputy Director,
Lupus Research Laboratory,
The Rayne Institute,
St. Thomas' Hospital,
London SE1 7EH, UK.

References
2. Vermielen J, Blockmans D, Spitz B, Deckmyn

INDUSTRIAL RHEUMATOLOGY AND THE SHOULDER

The shoulder is the most mobile joint in the human body [1] and limitations of this movement—particularly if they are associated with pain—lead to loss of working time and even premature retirement for affected employees in manual occupations and indeed for many office workers as well. Such conditions may be described as the painful arc syndrome [2], supraspinatus syndrome, and glenoid capsulitis. These syndromes may occur alone or in association with tension of the neck which in turn may merge imperceptibly with pain in the suprascapular and upper dorsal regions, with the site depending on whether or not pain arises locally or is referred from a nerve root or other spinal source [3]. Various collective terms have been used to describe these pains, e.g. cervicobrachial syndrome [4], neck and upper limb disorders [5], neck–shoulder problems [6], repetitive strain syndrome [7], and shoulder girdle pain [8]. So far as can be judged from the literature, these terms are often used synonymously.

Syndromes of the cervico-scapular region which are well known to rheumatologists, neurologists and orthopaedic surgeons and which are recognized by them as separate entities present problems to those seeking to study occupational aspects of this field because of semantic difficulties and in particular because of the manner in which the rubrics are classified in the International Classification of Diseases (ICD) [9, 10].

Not only is there a general lack of specificity of diagnostic labelling, but there are inconsistencies in groupings. Thus shoulder arm/hand syndrome is grouped with cervical problems under the general heading of dorsopathy, while shoulder girdle syndrome, supraspinatus syndrome and glenoid capsulitis are to be found with the enthesopathies. Terms such as bursitis, capsulitis, disc disease and spondylosis affecting the neck and shoulder cannot be distinguished from their counterparts in the lower back (or elsewhere) unless recourse is made to the fourth digit of the ICD, and even then only if the diag-