Hughes Syndrome

Second Edition

M. A. Khamashta (Ed.)

Hughes Syndrome

Antiphospholipid Syndrome

Second Edition

With 80 Figures

Springer

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Artwork marked with 🕮 symbol throughout the book is original to the 1st edition (Khamashta MA. Hughes Syndrome: Antiphospholipid Syndrome. Springer-Verlag London Ltd. 2000) and is being republished in this 2nd edition.

A catalogue record for this book is available from the British Library

Library of Congress Control Number: 2005926817

ISBN-10:1-85233-873-3 Printed on acid-free paper
ISBN-13:978-1-85233-873-2

ISBN 1-85233-232-8 1st edition

First published 2000
Second edition 2006

Printed in Singapore (EXP/KYO)

9 8 7 6 5 4 3 2 1

Springer Science+Business Media
springeronline.com

To my parents, Andrawes and Azizeh,
who have supported me throughout my life
and continue to inspire me to achieve.

Foreword to the Second Edition

The studies and discussions presented in the second edition of the *Hughes Syndrome* text had their beginning with a 1983 *British Medical Journal* publication entitled "Thrombosis, abortion, cerebral disease and the lupus anticoagulant." In the mid-20th-century, it was recognized that some patients with systemic lupus erythematosus had biological false positive serological tests for syphilis, often coincident with the presence of an anticoagulant in plasma and the some of these patients (particularly ones with somewhat atypical of patterns of lupus) paradoxically manifested an increased incidence of procoagulant complications. Nothing much was made of these associations, however, until Graham Hughes, author of the above citation, applied his talents of astute bedside observation, knowledge of disease mechanisms, imagination, and a "bloodhound" instinct for following relevant clues. Graham and his colleagues early-on documented vasculopathy as basis for the diffuse (variable) pathology characteristic of the syndrome; evidence that procoagulant features were mediated by antiphospholipid autoantibodies (aPL) followed. Over the past two decades, investigators around the world have turned their attention to the study of the Hughes syndrome. (Contributors to this text include 83 clinicians and/or scientists from 13 countries in Europe, the Americas, Near East, and Asia. They represent more than a dozen clinical subspecialties and several basic science disciplines; professionals and students in these fields will need access to this book, whether in institutional libraries or personal collections – good news for the publisher.)

Truly rational treatment and/or prevention of the Hughes syndrome will await more precise knowledge of its pathogenesis but the recognition in the 1980s that ischemic and necrotic lesions in affected organs are secondary to thrombosis rather than to inflammation played a significant role in improved management of the illness and avoidance of inappropriate therapy. Beyond anticoagulation, there is enormous potential for discovery of more specific (and potentially more effective) therapies based on better definition of the complex humoral and/or cellular events activated by aPL. For example, studies by Giradi and Salmon (described in Chapter 31) demonstrated that blockade of the complement system prevented fetal loss and thrombosis in an animal model of the Hughes syndrome, extrapolation to clinical trials of complement blockade should be forthcoming.

I would like to address the issue of terminology for this illness, herein designated the "Hughes syndrome." I have already referred to the historical role Graham Hughes played in describing the syndrome, the recognition of

clinical-pathological associations, and the relationship to aPL (reviewed in more detail by Munther Khamashta in Chapter 1). This alone, in my judgment, justifies acceptance of the eponym "Hughes syndrome" rather than "antiphospholipid syndrome." There are other rationales for that recommendation: (1) the precise molecular target of aPL remains a subject of study (beta 2 glycoprotein-1 versus phospholipids), (2) in some patients the illness and presence of aPL are disassociated over time, and (3) the longstanding use of eponyms for other vasculopathies (e.g., Wegener, Churg-Strauss, Kawasaki, Henoch-Schöenlein, Behçet, Takayasu) have utility in recognizing individual clinical and pathological patterns of disease and management objectives.

Finally, I would like to draw attention to a short chapter at the end of the book, "The Future of Hughes Syndrome." In this chapter, Michael D. Lockshin summarizes recent progress in our understanding of the problem and, more importantly, identifies areas of ignorance and special opportunities for study. It is an exciting time for seeking new insights regarding the pathogenesis and management of the Hughes syndrome; this revised reference text will be an invaluable resource for anyone engaged in such inquiries.

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Foreword to the First Edition

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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Prologue to the First Edition

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 specialities.

From the early days in the late 1970's and early 1980's, 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

Prologue to the Second Edition

"*There are two 'new' diseases of the late twentieth century, AIDS and APS*"
Miquel Vilardell, Dean of Medicine of the University of Barcelona

Munther Khamashta deserves plaudits for his contributions to this corner of medicine. He has not only published numerous original papers on the syndrome, notably in the field of recurrent pregnancy loss, but he has also brought together colleagues with clinical and research expertise. The first edition of his book was a triumph – an example of clinically-based research which has had a major direct impact on medical practice.

In the 5 years since the first edition, there has been a dawning realisation of the extent of the impact of the antiphospholipid syndrome in so many branches of medical practice – in Alzheimer's, in multiple sclerosis, myocardial infarction, movement disorders, leg ulcers, infertility, renal and cardiac transplantation, avascular necrosis, ischaemic fractures – and even more so with the original pillars of the syndrome – stroke, TIA, DVT, pulmonary hypertension, and recurrent pregnancy loss.

Many of us working in this field have felt frustration at the seemingly slow recognition of its importance. However, things are changing. The number of research publications, reviews and conferences is increasing. In our own clinic, the number of referrals of patients with Hughes Syndrome now promises to overtake those with lupus.

In the original description of the clinical syndrome back in 1983, I wrote…. "For those of us hardened into nihilism by years of study of various autoantibodies in SLE there is a rare sense of excitement at the implications of the associations now being reported".

Twenty-two years later, this sense of clinical excitement has not waned.

Graham Hughes
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Section 1
Clinical Aspects

1 Hughes Syndrome: History

M. A. Khamashta

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.
>
> 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:
>
> 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.
>
> 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.
>
> 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.
>
> 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.
>
> 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 the early 1980s my team then at Hammersmith, collected large numbers of patients who had the syndrome, yet did not meet the classification criteria for lupus – we called these patients "anticardiolipin syndrome" – and changed the name to the antiphospholipid syndrome when it was clear that these patients' sera were also cross-reactive with other phospholipids such as phosphatidylserine [8–10].

So, in the few years between 1983 and 1987, our description of the syndrome included recurrent fetal loss [11], livedo [7], renal thrombosis [12], strokes [13], liver thrombosis including Budd–Chiari syndrome [14], myelopathy [15], chorea [16], bowel infarction [17], thrombocytopenia [18], pulmonary hypertension [19] and dementia [20].

The clinical collaborators included Margaret Byron, Bernie Colaco, Genevieve Derue, Mee-Ling Boey, 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 (*Lancet*) paper on the assay for anticardiolipin antibodies [21] which paved the way for the development of the enzyme-linked immunosorbent assay (ELISA) [22] and the widespread testing and recognition of the syndrome.

In his 1983 Prosser–White lecture, Graham Hughes emphasized his view that many of the patients did not have classic lupus, and deserved separate consideration as a syndrome [7]. His group, in the early 1980s, published a number of reports which associated aPL with the syndrome *outside* of systemic lupus. He reported aPL in Behçet's disease, idiopathic transverse myelopathy and Guillain–Barré syndrome [23], idiopathic thrombocytopenia [18], migraine, epilepsy [24], heart valve disease [25], and Addison's disease [26]. Graham Hughes's view was that this was most certainly a "distinct" syndrome which occurs in ANA-negative lupus erythematosus (LE) patients, atypical lupus patients, and, as expected, individuals with no lupus at all [7]. In 1987 his group was the first to introduce the term *antiphospholipid syndrome* and *primary antiphospholipid syndrome* [10] and 2 years later, in 1989, two large series of patients were published, one by his group [27] and another by the group in Mexico [28], which confirmed and detailed the earlier clinical descriptions.

In 1990 the next major advance, when three groups [29–31] reported that aPL required a plasma protein "cofactor" to bind cardiolipin on ELISA plates. β_2-glycoprotein I was identified as this cofactor. Since then, a number of "cofactors," including prothrombin, have been described [32]. The binding of antibodies to the antigen site is clearly complex and dependent on molecule configuration. Studies using monoclonal antibodies have, for example, suggested binding to a trimolecular site including phospholipid, protein C and cofactor [33]. It is now felt that the cumbersome term *phospholipid-cofactor syndrome* is probably wrong.

From Osler on, many observers of lupus have recognized thrombosis as a feature in some patients. Similarly, many other features, including thrombocytopenia and recurrent miscarriage, are well recognized as features of the disease. Historically, the "oldest" immunological finding in SLE is the Wasserman reaction. In 1952, Moore and Mohr recognized that their false positive (BFP-STS) syphilis tests could occur in lupus [34]. In 1957, Laurell and Nilsson [35] found that the "lupus inhibitor" was frequently associated with BFP-STS. Bowie et al [36] in clinical studies of lupus, reported thrombotic lesions in patients with a circulating anticoagulant. Beaumont et al in 1954 [37] were the first to report a patient with lupus anticoagulant and recurrent abortions. This was followed by similar observations by Nilsson et al [38] 20 years later and by Soulier and Boffa [39] 5 years after that.

This volume acknowledges the many who have worked so hard to bring recognition to the syndrome. To Nigel Harris and Aziz Gharavi – involved from the early days – to the dozens of research fellows who have trained in our laboratory, and whose names are associated with so much of the APS literature; to the late Donato Alarcon-Segovia, for his enthusiasm in endorsing the syndrome with his surveys of his own lupus patients; to Takao Koike, for providing so much to the studies of β_2-glycoprotein I; to Marie Claire Boffa, for her collaboration and organizing ability in setting up collabortive workshops; and to Yehuda Shoenfeld for contributing so much momentum, especially through his animal model studies, to our knowledge of the syndrome.

The ripples continue to spread. The world of transplantation is involved with huge implications for renal, liver, and cardiac transplantation [40], orthopaedics is embraced, not only in the predilection for avascular necrosis, but in the recent striking finding of spontaneous metatarsal and other bone fractures [41]. Internal arterial ischemia has embraced Hughes Syndrome as a possibly important cause of reno-vascular hypertension [42] and celiac axis stenosis as a "new" link to gastrointestinal symptoms [43]. In the world of neurology the ramifications include multiple sclerosis, memory loss, migraine, and even sleep disorders [44]. In dermatology, the importance of livedo, described in Hughes' original papers, is recognized, as is the contribution to chronic leg ulcers.

This syndrome is common. Many physicians ask: "Where were all these patients before?" They were always there – in lupus clinics, in migraine clinics, in anticoagulant clinics with strokes, with multiple sclerosis, and with a gamut of vascular problems. It is also probable that many, many patients – notably those with memory loss or subtle neurological deficit – remain undiagnosed.

The description of the APS by Graham Hughes has had an impact on patients in all corners of medical practice.

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2 Antiphospholipid (Hughes) Syndrome: An Overview

David P. D'Cruz

Introduction

The cardinal features of the antiphospholipid syndrome (APS), first described in1983 by Dr Graham Hughes and his team at the Hammersmith Hospital, included recurrent arterial and venous thromboses, fetal losses, and thrombocytopenia. Although a wide variety of clinical features have been added over the last 22 years, these major features have stood the test of time. The aim of this chapter is to give a clinical overview of the spectrum of these clinical features, the assessment of aPL, and their impact on morbidity and mortality.

Demographics

APS is now recognized as a common disorder and is certainly not a "small print" disease. Its importance lies in the fact that once diagnosed, this a treatable condition. The difficulty is that for many patients diagnosis is often delayed, sometimes for years, with consequent disability, loss of livelihood, inability to start a family, or even death.

The prevalence of antiphospholipid antibodies (aPL) in otherwise healthy populations is less than 1% and up to 5% in older healthy populations. In autoimmune diseases, especially systemic lupus erythematosus (SLE), however, the prevalence is much higher. There have been several large studies of the prevalence of aPL in SLE patients. Perhaps the largest is the Euro-Lupus study that found a prevalence of 24% IgG anticardiolipin antibodies (aCL), 13% IgM aCL, and 15% lupus anticoagulant (LA) in a cohort of 1000 patients with SLE [1]. The prevalence of aPL and definite APS may increase with longer follow up, further pregnancies, and repeat testing for aPL. Thus, Perez-Vazquez et al showed that the prevalence of APS increased from 10% to 23% after 15–18 years in a large cohort of SLE patients [2]. A further study of 1000 APS patients has detailed the clinical features of the disorder [3].

Definition and Classification of APS

An international consensus statement on classification criteria for definite APS was published after a workshop in 1998 (Table 2.1) and validated [4, 5]. These

Table 2.1. Classification criteria for the antiphospholipid syndrome.

Clinical criteria

1. Vascular thrombosis:
   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th weeks of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   (b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency or
   (c) Three more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic, or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/ or IgM isotype in blood, present in medium or high titre, on two or more occasions, at least 6 weeks apart, measured by a standard enzyme linked immunosorbent assay for β_2-glycoprotein 1-dependent anticardiolipin antibodies.
2. Lupus anticoagulant present in plasma on two or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

classification criteria were developed for use in research studies rather than as diagnostic criteria which have to date not been developed. Other well-recognized features of APS, such as thrombocytopenia, hemolytic anemia, transient ischaemic attacks, transverse myelitis, livedo reticularis, valvular heart disease, demyelinating syndromes, chorea, and migraine, were not thought to have as strong an association as the final criteria and were excluded as classification criteria, possibly resulting in lower sensitivity but higher specificity [5]. In clinical practice, however, the physician should still consider the diagnosis and commence treatment according to clinical judgment after exclusion of other causes of these clinical features.

There are numerous traps for the unwary and many other conditions can be associated with aPL but are not necessarily associated with thrombosis. Thus, aPL may occur in infections such as human immunodeficiency virus (HIV) and malignancy and may also follow exposure to certain drugs. aPL in these circumstances are not necessarily pathogenic and these conditions should therefore be considered in any differential diagnosis of APS.

Indications for aPL Testing

There is a compelling case for aPL to be tested routinely in all patients who are newly diagnosed with an autoimmune connective tissue disease, especially SLE or Sjögren's syndrome, because the prevalence of aPL in these disorders ranges between 30% and 50% [6]. The finding of aPL at disease onset may have significant consequences later in the disease course in terms of predicting morbidity and mortality [7]. In other clinical contexts, patients who suffer thrombotic events at relatively young ages should also be considered for testing. Thus, patients with strokes,

Table 2.2. Indications for the measurement of antiphospholipid antibodies.

Connective tissue disease especially SLE
Venous/arterial thrombosis before the age of 45 years
Thrombosis after trivial provocation
Association of arterial and venous thrombosis
Association of thrombosis and fetal loss
Recurrent events
Family history
Thrombosis in an unusual site: retinal vein, portal, cerebral venous sinus, renal vein
Recurrent superficial thromophlebitis
Recurrent miscarriage
Coumarin-induced skin necrosis

myocardial infarctions, and venous thromboses under the age of 50 may be at risk of further thrombotic events if they are aPL positive. Similarly, women with pregnancy morbidity should also have aPL measured. There is a wide spectrum of aPL-related pregnancy morbidity, including miscarriage, fetal death, intra-uterine growth restriction, intra-uterine death/still birth, pregnancy-induced hypertension, pre-eclampsia, and eclampsia. There is increasing evidence though that other thrombophilic disorders may also be associated with obstetric problems [8].

The timing of measurement may be important. Some authors have suggested that aPL may be consumed during a thrombotic episode, though this remains controversial. Alternatively, due to endothelial activation and exposure of cryptic antigens, aPL may appear after the thrombotic event as an "epiphenomenon" [9]. For these reasons aPL should be measured between 6 weeks and 3 months post-thrombosis to confirm results. Steroid therapy and the development of the nephrotic syndrome may also be associated with a falsely negative result [10, 11].

A recent intriguing paper has suggested that aPL may appear many years prior to the diagnosis of an autoimmune connective tissue disease such as lupus. Moreover, aPL-positive patients appeared to be at risk of more severe lupus later in the disease course [12]. This data is in keeping with their previous findings for anti-nuclear antibodies appearing long before the onset of clinical features of SLE. These studies suggest that immune dysregulation leading to autoantibody production may precede the appearance of symptoms by many years.

What Should Be Measured?

The recommendation is that both IgG and IgM aCL isotypes should be tested as well as LA. The significance of IgA aCL antibodies remains controversial but may be more relevant in SLE populations with African ancestry in contrast to Caucasians [13, 14]. The relevance of IgA aCL is discussed in detail elsewhere in this book. Although aPL testing has been standardized, there remain major inconsistencies when standard sera are sent to various laboratories. Testing for LA is also inconsistent but there seems to be a consensus that aCL are sensitive and LA testing is more specific in the diagnosis of APS. Anti–β_2-glycoprotein I antibodies correlate well with clinical features of APS as well as with other aPL and will be discussed in detail in this book. However, most routine laboratories do not offer anti–β_2-glycoprotein I

antibodies because in general there is no added value above conventional aPL testing and the assay lacks standardization.

Prevalence of aPL

General Population

The prevalence of aPL in the general population is low. Large studies have shown prevalences of between 2% and 7%. For example, in 543 blood donors under 65 years of age, Fields et al found an aCL prevalence of 2% [15]. The Antiphospholipid Antibodies in Stroke Study (APASS) Group also found a prevalence of aCL in 4.3% of 257 hospitalized non-stroke patients with a mean age 66 [16]. This was similar to the prevalence of 7.1% for at least one positive aCL in 1014 in-patients studied by Schved et al with a mean age of 66.7 years: the most frequent associations were with carcinoma or alcohol abuse [17].

Elderly

Many autoantibodies become more prevalent with increasing age and aPL is no exception. Fields found that 12% of 300 healthy individuals older than 65 years had IgG or IgM aCL antibodies and that there was an association with positive antinuclear antibodies (ANA) but not rheumatoid factor [15]. The significance of these autoantibodies remains unclear and could be related to the increasing prevalence of associated conditions in the elderly, such as malignancy and drug treatment.

Venous Thromboembolism

In patients with unselected venous thromboembolism, the prevalence of aCL varies from 3% to 17% and LA from 3% to 14%. The highest prevalence of 17% was found by Schulman et al, who tested 897 patients with venous thromboembolism as part of a treatment trial with a follow up of 4 years, in whom aCL were tested 6 months post–deep vein thrombosis (DVT). Interestingly, of 20 recurrent episodes, aCL was negative in 14 at the time of the recurrent episode [18].

Arterial Thrombosis

In the situation of stroke, Nencini et al found 18% of young patients, mean age 38 years, were positive for aPL (LA and aCL), whereas the APASS study found 9.7% of first stroke patients had a positive aCL. In myocardial infarction the prevalence of aCL is between 5% and 15% [19, 20].

Fetal Loss

There is a wide range of prevalences of aPL in otherwise healthy women who have had pregnancy morbidity, ranging from 7% to as high as 42%. The reasons for this are discussed in more detail elsewhere in this book.