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Introduction: What Are Autoimmune Diseases?

The immune system forms the ‘army’ which protects the human body against invaders. In any given moment, our body is exposed to the attack of various infectious agents including bacteria, viruses, fungi and parasites. These infectious agents reside on the skin, within the gastrointestinal tract and the mouth. Upon their invasion, our immune system protects our body in order to eliminate the intruders and fight disease. A competent immune system is obligatory for healthy and long life; indeed, in several inherited diseases in which the immune system is impaired, or alternatively in acquired immunodeficiency states such as AIDS, the affected person has severe infections and is more likely to die early due to one of these infections. Among the ‘troops’ of the immune system, there are T lymphocyte cells which help to identify the intruders, sometimes also directly to kill them, whilst in other times to activate other cells to do that job, B lymphocyte cells which produce the antibodies which bind the intruders and neutralize it, and macrophage cells which can practically eat the thus eliminate the infectious agent.

Autoimmune diseases (AID) are the outcome of abnormal activity of the immune system. Their meaning is auto= self immune reaction, or in other words, the activity of one’s immune system against himself. Due to various reasons including genetic factors and environmental factors as well (including infectious agents), the activity of the immune system is impaired, and part of it is directed against the self. (Figure 1).

There are many AID, some are rare but others are very frequent. Diabetes mellitus occurs following gradual damage to pancreatic cells which secrete the hormone insulin by T lymphocyte cells. Hyper- or hypothyroidism occurs following cells or autoantibodies directed to the thyroid gland. In case of immune-mediated thrombocytopenia, autoantibodies bind to blood platelets (which function in coagulation) and lead to their enhanced destruction, to low-platelet count and to bleeding diathesis. One of the fascinating AID is systemic lupus erythematosus (SLE) in which both cells of the immune

Figure 1. Autoimmune disease are usually the result of a combination of hereditary factors and an environmental factor which translates the hereditary tendency into a disease. This factor can be any infectious agent, various medications, or stress.
system and many autoantibodies occur. This disease affects women nine times more than men, usually at reproductive age, and it might be characterized by various clinical manifestations such as arthritis, skin eruption, renal damage, oral ulcers, photosensitivity, pericarditis and pleurisy, epilepsy, and cytopenia.

The treatments of AID include non-specific therapies for immunosuppression, or in other words, to suppress the activity of some parts of the immune system which acts against the self. These drugs include corticosteroids, cyclophosphamide, methotrexate, intravenous immunoglobulins (IVIg), or antibodies to cytokines (which are secreted from cells of the immune system and aggravate disease), or alternatively drugs which supplement the deficiency caused by the disease (i.e. insulin in diabetes, thyroxin in hypothyroidism).
Chapter 1: The Antiphospholipid Syndrome (APS) — General Features

APS is a relatively ‘young’ syndrome which has been defined only 20 years ago. Why is it a syndrome? APS includes various of clinical manifestations. Why antiphospholipid? The syndrome is characterized on the one hand by clinical manifestations, but on the other hand by the presence of one or more autoantibodies to phospholipids, a component of human cells envelope. These autoantibodies help to diagnose APS, but they also have a pathogenic role in the syndrome, as they are not just a sign for APS but also probably cause it (Figures 2, 3).

**Figure 2.** (top right) The most detailed book of APS which was edited by Ronald Asherson from South Africa, Ricard Cervera from Spain, Jean Charles Piette from France, and Yehuda Shoenfeld from Israel. This book contains all the relevant data of APS including the clinical manifestations, treatments, and bibliography.

**Figure 3.** (right) Another book of APS edited by Dr. Khamashta from London, the student and colleague of Prof. Graham Hughes which was the first to describe APS, a syndrome which was named after him. The book cover represents four systems affected in APS: a computerized tomography of the brain demonstrating brain infarction (CVA), picture of skin with livedo reticularis, heart valve disease, and reference to recurrent pregnancy loss.

**Historical Background**
Identification of antiphospholipid antibodies (aPL) and their association with the main clinical features of APS (vessel thrombosis and recurrent pregnancy loss) began in the early 1960s. At first, several patients having AID and also several healthy subjects had **false positive test for syphilis** (i.e. a positive blood test in the absence of syphilis). In 1952 the coagulation inhibitor **lupus anti-coagulant** (LAC) was identified in both healthy subjects and patients, mainly in those having
the false positive test for syphilis. LAC was absent from patients having syphilis. This name is a misnomer as most patients having LAC do not have lupus (SLE), and even though it causes anti-coagulation in blood tests, its activity in human body is mostly opposite: it enhances coagulation and leads to thrombosis. In the early 1980s a test was developed for detection of anti-cardiolipin antibodies (aCL) in patients’ plasma. Similarly to LAC, the presence of aCL was also associated with thrombosis and recurrent pregnancy loss. In the next years, it became clear that these autoantibodies are similar but not identical (Figure 4). In 1990 it has been found that a cofactor is required for aCL to bind its target: cardiolipin. This factor was β2-glycoprotein-I (β2GPI), which is considered the actual autoantigen in APS to which aCL really bind. Upon progression in research, it has become clear that aPL can cause the various clinical manifestations of APS, and therefore they are a marker of the syndrome, but probably also cause it.

- Why do I have a false-positive test for syphilis if I do not have syphilis?
- The test is only false positive. aPL bind the lipids found within the test kit and turn the test result into positive whilst there is no syphilis.

In parallel to developments of aPL, a close relationship was established between them and thrombosis. In 1963, it has been surprisingly reported that patents having LAC, which seemed in laboratory tests as a coagulation inhibitor, had thrombosis-intra-vascular blood clotting, and do not have bleeding diathesis. In 1954, the first patient having LAC and seven recurrent abortions has been reported. In 1983 the clinical manifestations of thrombosis and recurrent pregnancy loss were connected with aPL into a syndrome. Through the years, the definition of APS has expanded, and nowadays many other autoantibodies and clinical manifestations of APS are known.

Figure 4. One of the authors of this book (Prof. Shoenfeld) together with Prof. Graham Hughes, head of the lupus and APS clinic in St. Thomas hospital in London. In this clinic over 2,000 lupus and APS patients are being treated.
Classification Criteria of APS

A definite diagnosis of APS requires the presence of at least one clinical criteria and one laboratory criteria.

The Clinical Criteria:
1. Thrombosis — at least one episode of thrombosis within artery, vein or small vessels within any organ or tissue.
2. One of the following during pregnancy:
   a. One or more pregnancy loss after 10th gestational week, when anatomical, genetic and hormonal reasons for abortions have been excluded.
   b. One or more episode of a pre-term delivery before 34th gestational week, due to severe pre-eclampsia or severe placental insufficiency.
   c. Three or more recurrent pregnancy loss before 10th gestational week, when anatomical, genetic and hormonal reasons for abortions have been excluded.

The Laboratory Criteria:
1. Detection of IgG or IgM aCL in medium to high titers, in two different measurements at least six weeks apart.
2. Detection of LAC in two different measurements at least six weeks apart.

The clinical manifestations of APS are numerous and various, and by far exceed those used for APS definition. Usually APS patients have more than one clinical manifestation. However, in order to definitely diagnose APS, the above-mentioned criteria should be met. Patients having a laboratory criteria for APS in the absence of clinical criteria, but yet have a clinical manifestation suggesting the presence of APS, have probable APS even though they are not included under APS definition. Similarly, APS is characterized by many aPL, and therefore patients having a clinical criteria for APS but without a laboratory criteria, but do have another autoantibody which is found in APS, also have probable APS even though they are not considered having definite APS.

Primary and Secondary APS

Primary APS is found in patients without an associated disease, or without evidence of any agent that could have induced production of aPL. Many of the cases of idiopathic recurrent pregnancy loss in the past are now known to be part of APS upon detection of aPL. Secondary APS, on the other hand, is found in patients with another disease or in those having another cause suspected as the one which induced aPL production. It does not mean that secondary APS differs from primary APS, as the clinical manifestations of APS in both cases can be identical.
What are the conditions which accompany secondary APS?

1. AUTOIMMUNE DISEASES

SLE is the AID most commonly associated with secondary APS (Figure 5). About 40% of SLE patients would eventually develop secondary APS (Figure 6). Other AID which can cause secondary APS include: rheumatoid arthritis, Sjogren’s syndrome, scleroderma, vasculitis, diabetes mellitus and Crohn’s disease.

I have primary APS. Am I prone to have also SLE?

Generally no. Most primary APS patients will not have SLE in the future, even though few such cases have been described even 19 years following diagnosis of primary APS. Since some of the manifestations of APS are similar to those of SLE, the physician should undertake several tests in order to differentiate primary APS from APS associated with other conditions, including SLE.

I have SLE. Am I prone to have also secondary APS?

Yes. The prevalence of aCL among SLE patients is 16%–51%, and LAC can be found in 11%–30% of them. Close to 40% of SLE patients would eventually develop secondary APS, and thus the presence of aPL in SLE patients should be regarded as a risk factor for the manifestations of APS, thrombosis and abortions.

2. MALIGNANCIES

Several of the clinical manifestations of APS, and mainly thrombosis, can accompany several cancers. Some of the malignant conditions are associated with a pro-thrombotic tendency. It is possible that aPL are the explanation of some of these conditions. The most common malignant diseases associated with secondary APS are lymphoma, leukemia, other cancers of the blood, thymoma, and carcinomas of the lung, ovary, kidney, cervix and prostate.
I have primary APS. Should I be worried since I might have an occult malignancy?
Usually no. Following the diagnosis of primary APS a search for cancer is not indicated unless there are signs and symptoms suggesting its presence (i.e. prolonged fever, weight loss, elderly).

I have a prostate cancer. Am I prone to have secondary APS?
Probably no. Thrombosis and other features of APS occur in the minority of cancer patients, but once these features appear one should suspect the presence of secondary APS and look for aPL.

3. DRUGS
Several drugs can cause the appearance of aPL. These include oral contraceptives, procainamide, phenothiazines, ethosuximide, phenytoin, quinine, chlorothiazide, hydralazine and interferon-alpha. Some of these drugs also induce autoantibodies and a lupus-like disease.

My doctor prescribed me procaineamide. Should I be worried that I would have APS?
No! aPL appear in the minority of patients treated with the above-mentioned drugs. Moreover, even though thrombosis has been described in some patients, in most cases that presence of aPL following drug administration is not accompanied with any clinical picture.

4. INFECTIOUS AGENTS
Many infectious agents can occasionally induce aPL, mainly aCL. These include hepatitis C virus, varicella virus which causes chickenpox, parvovirus B19 which causes anemia and fever, human immunodeficiency virus which causes AIDS, cytomegalovirus which causes infectious mononucleosis, several bacteria, and leptospira (Figure 7). Mostly these infectious agents do not cause APS as they induce aPL which


Figure 7. Several articles describing various infectious agents which are associated with APS induction. These include the cytomegalovirus and Epstein-Barr virus which cause infectious mononucleosis, human immunodeficiency virus which causes AIDS, the hepatitis C virus which causes infectious hepatitis, the adenovirus which causes a febrile illness, and the bacteria which causes leprosy.
do not bind β2GPI and thus do not cause thrombosis. However, in some of the cases of catastrophic APS, infection preceded the clinical manifestations.

Is APS contagious?
Definitely no! It is absolutely safe to stay near a patient having APS, as the syndrome is not infective and does not spread from person to person.

**APS — A Prevalent Disorder**
The prevalence of aPL in the general population is around 2–5%. The prevalence of many autoantibodies increases with age, and the same is true for aPL as their prevalence in the elderly can be very high. Since APS is characterized by various clinical manifestations, it is difficult to estimate its real prevalence. However, APS is the cause of a significant number of thrombotic episodes and recurrent abortions (Figure 8). In the general population, APS is the leading cause of acquired hypercoagulability (blood tendency to coagulate and form thrombosis). aPL are found in higher frequency in several manifestations attributed to blood hypercoagulability (sticky blood):

- The prevalence of aPL among patients having venous thrombosis (usually involving deep veins of the thigh and legs) is between 5–30%. Finding of aPL posses a risk for first event of venous thrombosis, recurrent events and death.
- The presence of aPL is a risk factor for myocardial infarction (heart attack).
- Stroke (either permanent= cerebrovascular accident, or transient= transient ischemic attack) is the most frequent feature of arterial thrombosis in APS. aPL are found in 2–46% of patients less than 50 years of age having stroke. Approximately, one in every five strokes in patients under 40 is due to APS. Most studies also report high prevalence of aPL in older stroke patients.

*Figure 8. APS is discussed in international conferences. The recent meeting was organized by Prof. Shoenfeld in Taormina, Sicily. The picture represents the opening page of the meeting with the triangular sign of the girl with 3 legs. 600 physicians and researchers attended this meeting, and discussed the various aspects of the syndrome. The next meeting would take place in November 2004 in Sydney, Australia.*
• One of four women having two or more spontaneous abortions have APS. The association between aPL and abortions is stronger in late pregnancy loss, but also exists in abortions before 10th week of gestation.

Thrombotic events are very frequent in the general population as a leading cause of disability and mortality due to heart attacks and strokes. One should suspect an association between these events and APS especially in young patients having thrombosis, and in any women having recurrent pregnancy loss. Establishment of an association between the clinical manifestations and aPL is of highly importance since a proper treatment would be able to prevent in most cases recurrent events and even death.

**The Genetic Background of APS**

Most AID have a genetic background, but this hereditary component is not as obvious as diseases which are transferred from a parent to his children in half of quarter of cases. On the other hand, it is relatively common that members of the same family would have different AID. For example, a mother might have hypothyroidism, her sister could have diabetes mellitus whilst her daughter having SLE. The conclusions of the genetic research in the field of primary APS is that this syndrome is significantly different in its genetic aspects from SLE (even though secondary SLE might occur during lupus). The genetic predisposition for APS is partially explained by markers called human leukocyte antigens (HLA). Some of these HLA molecules are related to aPL: HLA type DR4, DR7, DRw53, and DQB1*0302 are associated with the presence of aCL. The genetic background is also responsible for the structure of β2GPI; this structure in turn may induce the production of anti-β2GPI autoantibodies. The replacement of one amino acid in the structure of β2GPI could turn this molecule immunogenic and produce autoantibodies. The genetic findings in the research of APS can explain only partially the development of APS, and like in other AID, disease occurrence depends both on hereditary factors and environmental factors such as infectious agents.

**One of my family members has APS. Am I likely also to develop it?**

There is increased prevalence of APS among family members, even though the genetic background of the syndrome is not completely understood. Yet, the chances of a family member of an APS patient also to develop APS are low.
Chapter 2: The Clinical Manifestations

The clinical manifestations of APS are diverse and might include every organ in the human body (Figures 9, 10). Though the diagnosis of APS requires the presence of thrombosis or pregnancy morbidity, APS patients can have disorders in various body systems including every organ in the human body.

Figure 9. A diagram representing the clinical manifestations in 1,000 patients having APS. The common clinical manifestations are thrombosis, strokes, pregnancy failure, involvement of blood system, heart injury, and in addition damage to the lungs, eyes, kidneys, skin, joints, bones and abdominal viscera.
Figure 10. APS is a systemic disease which can affect every organ in the human body. Her major characteristics include: deep venous thrombosis, pulmonary emboli, myocardial infarction, stroke, livedo reticularis, heart valve disease, recurrent abortions, skin ulcers, impaired blood supply to the fingers, budd-chiari syndrome, and small vessel disease of the kidneys.
What Is thrombosis?
Normal blood perfusion in the human body requires patent vessels in order to ensure supply of blood, oxygen and nutrients (such as glucose) to the different organs. Thrombosis describes the process of formation of blood clots within a vessel which partially or completely stops blood flow distal to affected region (Figure 11). Thrombosis is a physiological process of highly important during injury upon vessel bleeding which must be stopped, and thus this process is life-saving. Under normal circumstances, several factors prevent unnecessary thrombosis (such as natural anti-coagulants). Thrombosis within vessels which supply blood to the brain, heart, kidneys or any other vital organ might be disastrous. APS is characterized by hypercoagulability and formation of thrombosis within vessels.

I had thrombosis of my thigh vein. Do I have APS?
Not necessarily. APS causes a significant number of venous thrombosis, but there are also other factors that might cause it. In some of the cases of venous thrombosis it is possible to identify factors which increased the risk of thrombosis such as immobilization following fracture or surgery, oral contraceptives, or cancer. Other cases of thrombosis are associated with hereditary hypercoagulability states, and there are still cases where the cause of thrombosis remains unknown (idiopathic). APS means thrombosis in the presence of aPL.

I have APS and I had an event of deep venous thrombosis in my thigh. Am I prone to thrombosis only in that region?
No. The pro-thrombotic tendency is general, and hence thrombosis is possible in every vein and artery, and requires further preventive measures.
I had deep vein thrombosis of my thigh. Should I avoid long-distance flights?
The immobility characterizing the seating position within long-distance flight predisposes for lower limbs thrombosis. If flying cannot be avoided, other predisposing factors should be minimized: stop smoking, do not take oral contraceptives, and drink more water. The risk for such thrombosis is higher during pregnancy. If you are not treated with anti-coagulants during flights, it is possible to consider administration of preventive treatment with low-molecular-weight heparin, according to physician’s decision.

What is embolus? Once the thrombus within the vessel detaches (partially or completely) it might flow further within blood and obstruct other vessels. The location of thrombosis is important in this case: arterial thrombosis can cause emboli in more peripheral arteries. For example, thrombus within the left ventricle of the heart or within the aorta can send emboli to the brain, intestines, kidneys or other organs and cause clinical manifestations according to the affected organ (Figure 12). On the other hand, venous thrombosis in the limbs can emboli into a larger vein, and then into the right side of the heart, and from then into the arteries of the lung causing life-threatening pulmonary embolism.

Figure 12. The association between heart valve disease and strokes. Heart valve disease can help produce blood clots within the heart. These blood clots can detach and be sent as emboli to the brain. This is one of the mechanisms of action of strokes in APS.
APS and the Heart

Case Report

A 25-year-old woman, usually healthy, suddenly felt chest pains. Since the pain did not resolve and was also accompanied by dyspnea and nausea — she admitted to the emergency room. Electrocardiogram examination revealed acute myocardial infarction (heart attack). Coronary angiography demonstrated obstruction of the left anterior descending artery. The obstruction was opened and an intra-arterial stent was placed in order to reduce the risk of re-stenosis. She was later found to have high titers of aCL.

Involvement of the heart in APS is associated with significant morbidity and mortality (Figure 13).

Coronary artery disease. This disease is found in many patients within the general population, and is the leading cause of death in the Western world due to myocardial infarction and other manifestations of the diseases coronary arteries which supply the heart. APS is associated with enhanced atherosclerosis.

Figure 13. The clinical manifestations affecting the heart in more than 100 patients having APS (out of a group of several hundreds). The most frequent clinical manifestations include heart valve thickening and heart valve dysfunction, myocardial infarction, heart valve vegetations, and chronic disease of the heart muscle.
Atherosclerosis is characterized by deposition of lipids and cells of the immune system within arterial walls, and once it occurs within the coronary arteries it results in coronary artery stenosis. During physical exertion, angina pectoris occurs due to the inability of these narrowed arteries to provide sufficient amount of blood to the heart. Angina pectoris is manifested by mid-chest pain, and it resolves following rest or use of vasodilating drugs. Some of the patients have unstable angina pectoris which is characterized by pain appearing also during rest, and it is caused due to almost complete obstruction of a coronary artery or alternatively due to complete arterial obstruction which spontaneously resolved. Atherosclerosis might lead to thrombosis within the coronary arteries and blockade of blood flow within these arteries. The part of myocardial muscle which is supplied by the obstructed artery is undergoing necrosis, and this is actually myocardial infarction (heart attack). It is usually manifested by chest pain that can radiate to other regions such as the arms, upper abdomen, and lower jaw. The pain is not relieved during rest, and might be accompanied with vomiting, perspiration and extreme weakness. Even though in some cases myocardial infarction can be mild and not lead to significant impairment of heart function, in other cases it can cause heart failure, dangerous arrhythmias and even sudden death. Myocardial infarction occurs in about 7% of APS patients, even though in different studies the prevalence of myocardial infarction was up to 30%. An objective evidence for coronary artery disease is found in 10% of APS patients who also have SLE. Apart from aPL, several risk factors contribute to cardiovascular diseases in these patients (smoking, hypertension, hypercholesterolemia, diabetes mellitus), and therefore treatment of these risk factors is of a great importance in these patients. The presence of aPL signifies an increased risk for cardiovascular diseases, and thus it is not surprising that even in the general population without APS the presence of these autoantibodies was associated with a two-fold increased risk for myocardial infarction. In addition, aPL could be detected in 5–15% of patients having acute myocardial infarction.

My father had an heart attack. Did he have APS?
Probably no. Heart diseases are very frequent in the general population, and their incidence increases with age and presence of certain risk factors (smoking, hypertension, diabetes mellitus, hypercholesterolemia). Occurrence of myocardial infarction at a young age is more characteristic of APS.
**Heart valves disease.** The heart valves regulate blood transfer within the heart (from atria to ventricles) and from the heart to the major body vessels (the pulmonary artery and the aorta). The most frequent manifestation of heart valve disease both in APS and in lupus is **heart valve thickening** (Figure 14). The valve most frequently involved is the mitral valve which regulates blood transfer from the left atrium to the left ventricle, followed by the aortic valve which regulates blood transfer from the left ventricle to the aorta and thereafter to the whole body (Figures 15,16). This injury is probably associated with the presence of aPL as it is more frequent in patients having high autoantibody levels (Figure 17). Thickened heart valves have impaired function. About quarter of APS and lupus patients have mitral valve injury which results in reverse blood flow from the left ventricle to the left atrium. This injury is significant in 5% of the patients and results in heart failure. Another kind of valve injury in APS is heart valve **vegetations.** These are verrucae which might interfere with blood flow through the heart valves, although usually they do not cause this manifestation. However, the vegetations form a site for bacterial overgrowth and development of bacterial endocarditis. Therefore, it is not surprising that aPL can

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**Figure 14.** The historical article of the two physicians Libman and Sacks that described in 1924 the heart valve disease in lupus patients.

**Figure 15.** Heart valve deformity which is characteristic for APS. The valve appears distorted with vegetations upon its surface.

**Figure 16.** Heart valve deformity is diagnosed by echocardiography. In this test, an electronic inducer is protruded into the esophagus in order to be close to the left heart atrium. The arrow points to a vegetation which occurs in APS.
be found in about 10% of patients with infection of the interior part of the heart (endocard): endocarditis. Another interesting manifestation in APS is pseudo-infective endocarditis which imitates the clinical manifestations of infective endocarditis with fever, heart valve vegetations, heart murmur, and splinter hemorrhages. However, no infective agent can be detected by blood cultures whereas medium to high titers of aPL can be found. These autoantibodies have important role in heart valve damage both in primary APS and in lupus, as they are found in 90% of lupus patients who have heart valve injury, and in only 40% of lupus patients without heart valve disease.

Cardiac thrombosis. APS is characterized by hyper-coagulability, and thus can manifest by a thrombus within cardiac chambers. This thrombus can cause severe heart dysfunction, as well as emboli to other organs with subsequent occlusion of vessels which supply the brain, kidneys and other vital organs.

Respiratory Manifestations in APS

Case Report

A 40-year-old man complained of pain and swelling of his right leg following an inter-continental flight. The pain spontaneously dissolved but recurred following a long-distance flight two years later. In the latter episode the pain was associated with shortness of breath. The patient was diagnosed as having a deep venous thrombosis of his thigh vein with pulmonary emboli, and treated with heparin. His blood test was positive for the presence of lupus anticoagulant. This autoantibody causes the hyper-coagulability which developed during the immobilization characterizing long-distant flights. The hypercoagulability led to venous thrombosis and subsequently to emboli to the lungs.
Pulmonary emboli. Vessels thrombosis is one of the most common features of APS (Figures 18,19). Deep venous thrombosis (usually of the lower extremities) is the most common manifestation of thrombosis in APS. About third of the cases of deep venous thrombosis are associated with pulmonary emboli. Depending on its size, the embolus occludes one of the arteries in the lungs and interferes with gas exchange so that blood cannot be adequately oxygenated. The clinical manifestations of pulmonary emboli include chest pain, dyspnea, tachypnea, decreased blood oxygen saturation, cardiac dysfunction and even sudden death.

Pulmonary thrombosis. This is a rare manifestation of APS. However, as thrombosis can occur in every vessel in the human body, it can also occur in one of the major arteries of the lung. The thrombosis can also affect multiple small lung vessels.

Pulmonary hypertension. The blood pressure within lung arteries is significantly lower than blood pressure in the arteries supplying the rest of the body. Increase in arterial lung blood pressure indicates a disease, can lead to lung dysfunction and even to death. Pulmonary hypertension occurs in 2%-3% of APS patients and is usually the result of recurrent pulmonary emboli.

Pulmonary hemorrhage. The lung nodes form the site in which gas exchange occurs between air and blood. Oxygen transfer into the blood and carbon dioxide transfer out of the blood occurs when lung nodes are filled with air. Hemorrhage into lung nodes occurs occasionally in APS and in lupus, and is characterized by cough, fever, dyspnea and hemoptysis.
Figures 20–23. Mice in the experimental models of APS.

20) Autoantibodies from the serum of patient having APS have been injected into these mice. The objective of the study was to provide proof for the pathogenic role of anti-cardiolipin in APS.

21) A figure of uterus from mice which were injected with irrelevant antibodies from a healthy subject. The embryos developed well within the uterus.

22) Uterus from a mouse which was injected with anti-cardiolipin antibodies. The uterus is distorted, and several scars represent embryos resorption, a phenomenon which is equal to recurrent abortions in human. By this study, Dr. Miri Blank and her colleagues from the Center of Autoimmune Diseases at Sheba Medical Center, Israel, provided proof for the pathogenic role of anti-cardiolipin in APS, as it can induce the different manifestations of diseases.

23) Hyper-coagulability in 2 different sites in an embryo which was adversely affected by anti-cardiolipin.

Figure 24. A microscopic picture of a placenta which demonstrates a characteristic injury in APS: small placental villi which do not develop well, and thrombosis within the placental vessels.
Recurrent Abortions, Pregnancy and Fetal Demise in APS

Some of the infertility cases remain unexplained. It has been suggested that part of these unexplained cases are caused by aPL. However, aPL classically cause recurrent abortions and obstetric complications.

Case report

A 35-year-old woman had a history of five recurrent abortions, and she was found to have medium levels of anti-cardiolipin autoantibody. Treatment was begun with aspirin and low-molecular-weight heparin during her 6th pregnancy, and she gave birth to healthy child at 36 weeks of gestation.

Recurrent abortions. 2%–5% of women of reproductive age experience two or more abortions. Pregnancy loss during any stage of pregnancy may be the first and occasionally the only sign of APS. The characteristics of pregnancy losses in the various research articles dealing with APS differ, but as a whole aPL are associated both with early and late pregnancy loss. Most cases of abortions in women with and without APS occur at early stages of pregnancy. Since APS is also associated with late pregnancy loss, the rate of women with this type of abortions is relatively high. The presence of aPL is important for the diagnosis, but it also has a prognostic significance. The subsequent abortion rate in a woman positive for aPL is as high as 90%, and significantly higher than women without aPL (Figures 20–23). This is the natural course of APS, but once patients receive prophylactic therapy their chance of giving birth to a healthy child significantly increases.

Pregnancy morbidity. Pregnancy is a physiological state, but it might be accompanied by some pathological complications. Some of these complications occur more often among APS patients. Pre-eclampsia is a complication occurring during pregnancy characterized by appearance of hypertension and proteinuria (excretion of protein in the urine) during pregnancy. This phenomenon poses a risk for the pregnant women and can be evolved into eclampsia with seizures, and it can also adversely affect the fetus. Pre-eclampsia is not a rare manifestation during pregnancy, but its frequency is higher among APS patients. In APS patients, pre-eclampsia usually occurs at an earlier stage of pregnancy and is more severe than in women without APS. Pre-term delivery is also frequently found among APS patients (approximately in 20% of the cases) and is usually the result of child birth induced by the physician due to pre-eclampsia and fetal growth retardation. This latter complication of APS is usually the result of placental dysfunction in APS (Figure 24), and it has been reported in 10%–30% of
the pregnancies of women having APS. aPL can also cause thrombosis during pregnancy in 5% of women which negatively affects maternal health and pregnancy.

I had several recurrent abortions and diagnosed as having APS. I did not have any other manifestation of this syndrome. Do I have an increased risk for thrombosis?

Usually yes. The presence of aPL indicates an increased risk for thrombosis in the future. However, there are women with APS who have recurrent abortions as the sole manifestation of APS.

**Cutaneous Manifestations**
- Livedo reticularis
- Livedo vasculitis
- Necrotizing purpura
- Leg ulcers
- Atrophic blanche
- Distal cutaneous ischemia
- Widespread cutaneous necrosis
- Peripheral gangrene
- Thrombophlebitis
- Hemorrhage

**Figure 25.** Skin manifestations of APS.

**Figure 26.** Livedo reticularis in various sites in the body.
Skin Manifestations

Skin involvement in APS occurs due to different pathogenic mechanisms, but is usually the result of small vessel thrombosis, thus affecting small arterioles and venules supplying blood to the dermis and sub-cutaneous fat. APS have various dermatological manifestations (Figure 25). The most frequent skin manifestation of APS is **livedo reticularis** which is characterized by a net-like reddish-blue discolorization (Figure 26). Occasionally a similar phenomenon can be found in healthy subjects following cold exposure. Livedo reticularis can be found in about quarter of APS patients, more in women than in men, and in higher frequency in patients having secondary APS associated with lupus. Other common skin findings in APS are **skin ulcers** which occur in 55 of the patients. They usually manifest as small and painful lesions with a diameter of 0.5–3 cm with a round- or star-shaped borders, circled by brown-purple border and intra-dermal hemorrhage. Skin ulcers usually present over the ankles and feet. As the ulcers heal they usually leave white scars surrounded by black pigment. **Superficial skin necrosis** can be found in 2% of APS patients, and evolves as skin eruption followed by black necrosis in the buttocks, limbs or face. This manifestation can also be found in other hyper-coagulability states, and sometimes APS patients having superficial skin necrosis have also another hyper-coagulability disorder which also contributes to thrombosis. Some of these patients have other autoimmune, malignant or infectious diseases.

**Multiple sub-ungual hemorrhages** can be a manifestation of various diseases, including for example endocarditis. They have been reported in 1% of APS patients, and are the result of thrombosis of the sub-ungual vessels, or from emboli sent from the heart. Another dramatic manifestation of APS is **digital necrosis** that occurs in 3% of the patients with APS, even though a higher rate have been also reported, up to 19% of the patients. The risk factor for this manifestation of APS are smoking, hypertension, and oral contraceptive use. Treatment of these risk factors can prevent other clinical manifestations of APS. **Superficial vessel thrombosis** can occur in 12% of APS patients, and it involves usually lower limb vessel thrombosis manifested by pain and local tenderness. Once thrombosis is persistent and affects the torso, it might be due to occult cancer states accompanied by aPL. Occasionally APS patients have skin lesions similar to those found in patients with inflammation of skin vessels (vasculitis).
The most frequent central nervous manifestation of APS (Figure 27) is stroke — thrombosis or disruption with blood supply to the brain with subsequent brain tissue damage since no oxygen can be supplied. Stroke can be the result of intracerebral thrombosis, thrombosis in the large vessels supplying the brain (the carotid arteries in the neck or the vertebral arteries in the spinal column), or alternatively due to emboli of thrombosis in the aorta or the heart. Stroke can lead to permanent vascular occlusion and destruction of the affected brain tissue (CVA- cerebro-vascular accident) and then most affected patients would have some degree of disability. However, the blood clot can spontaneously dissolve in some cases and then the manifestations would be only transient (TIA- transient ischemic attack). The outcome of stroke depends on the size of vessel which was blocked and on its location within the brain. The most frequent possible clinical manifestations of stroke include paresis or plegia (usually of the hand and leg of the same side), unilateral face plegia, difficulties in speech or understanding of words, loss of consciousness and even death. Among patients who had stroke, the presence of aPL is associated with a 2–7 times increased risk for stroke compared with patients without aPL. Whereas stroke is not a rare manifestation among elderly subjects, it usually occurs in APS among young adults, several decades prior to the general population. Another form of brain thrombosis is
venous sinus thrombosis. The venous sinuses are venous channels responsible for blood outflow from the brain. Thrombosis of the venous sinuses can be severe and lead to brain infarcts. Sneddon’s syndrome is defined as recurrent strokes and livedo reticularis (see the chapter “Skin involvement in APS”). The prevalence of aPL in Sneddon’s syndrome differs between several researches, but as a general rule they can be detected in about half of these patients; higher rates, up to 85% have also been reported (Figure 28).

Two years ago I experienced transient weakness of my arm and leg which returned to normal within two hours. Does it mean that I would not have permanent disability in the future?
Absolutely no! Transient ischemic attack signifies that the chance of having recurrent stroke is very high. The recurrent stroke can leave permanent disability (CVA) and can even result in death. Thus preventive measures should be started.

Dementia. This phenomenon is characterized by cognitive dysfunction, a decline in brain functions with memory disturbances up to inability to perform daily activities. Several diseases can lead to dementia, probably the most famous among them is Alzheimer’s disease. The pathogenesis of dementia in APS is recurrent brain infarcts resulting from minor events of thrombosis that over time manifest as dementia. It is also possible that aPL directly gravely affect brain tissue without the need to induce thrombosis. Continuation of thrombosis without appropriate treatment can cause recurrent and progressive brain damage with disruption of superior brain functions such as memory and cognition.

Epilepsy. The etiology of epilepsy is not clear in many cases. It is generally accepted that epilepsy manifested by seizures is due to some kind of brain injury. Some of lupus patients have epilepsy, and aPL were found associated with this manifestation. A possible pathogenic mechanism of epilepsy in APS is thrombosis followed by brain infarct and scar formation. The scarred brain tissue have a

Figure 28. Sneddon’s syndrome characterized by livedo reticularis and stroke. Most patients have elevated levels of antiphospholipid antibodies.
dysfunction with respect to signal transmission (such as that affecting muscular contraction) and thus can cause uncontrolled muscle action and practically to seizures. aPL might also have a direct effect of the brain that can promote epilepsy, such as decreasing the activity of the neurotransmitter GABA. Anti-cardiolipin autoantibody which is part of the spectrum of aPL was also found in increased frequency among epilepsy patients without previously known APS. **Depression, mood changes and psychosis** might also be associated with aPL, and there are few reports about increased frequency of these autoantibodies in those conditions.

**Migraine**. This is one of the most common manifestations of central nervous system involvement in lupus. Migraine can be classified into several types, but the most frequent presentation is a unilateral headache with vomiting and flashing lights. Migraine is also very frequent among APS patients, but aPL are not found in increased frequency in patients having migraine. Some cases of migraine evolve into complicated migraine in which paralysis can occur. aPL were detected in about a third of the patients with complicated migraine who had transient paralysis or brain infarct. Albeit there are not enough data, it is logical to conclude that even if aPL do not cause migraine, they can contribute to migraine complications.

**Myelitis**. This inflammatory process of the spinal cord is occasionally due to an autoimmune process. Few APS patients had transverse myelitis, which can be detected in about 1% of lupus patients. Once aPL are associated with transverse myelitis, their mechanism of action is probably thrombosis of the small vessels which supply the spinal cord, leading to infarct in a small part of the spinal cord, exactly in the same mechanism of action in which they cause brain infarcts. The clinical manifestations depend on the level of spinal cord affected, and can include paralysis below the level of injury, and urinary incontinence. Some of these cases can be successfully treated with anti-coagulation (as a part of other therapies).

**Hematological Manifestations of APS**

**Thrombocytopenia**. Blood platelets have a crucial role in blood coagulation. Formation of blood clots is an essential process in order to stop bleeding. Nonetheless, the very same process leads also to vascular occlusion and thrombosis. The platelets initiates blood coagulation, and their deficiency can cause hemorrhage into the skin and mucosae, and rarely into the brain. APS patients have thrombocytopenia in 20%–40% of the cases, but usually in its mild
form with a platelet count above 50,000 per milliliter (normal range: 150,000–450,000). Severe thrombocytopenia is found in the minority of patients, about 5%–10% of the cases. Severe bleeding accompanies the low platelet counts only rarely, and in these few cases an aggressive treatment should be undertaken. The prevalence of thrombocytopenia among APS patients is similar to that of lupus patients, and occasionally can be the first manifestation of APS (Figure 29).

I have APS with a low-platelet count. Am I at risk for thrombosis or bleeding? The main risk is for thrombosis due to aPL. The bleeding accompanying thrombocytopenia is usually mild, and severe bleeding cases are very rare in APS.
**Anemia.** This term stands for decreased red blood cell volume accompanied by low hemoglobin levels, and can be encountered in various pathological states, including APS. The pathogenic mechanism of anemia may be autoimmune by autoantibodies directed to autoantigens on red blood cells, leading to their destruction which usually takes place in the spleen. In some of the cases of autoimmune hemolytic anemia, aPL can be detected, usually anti-cardiolipin antibodies. Some of lupus patients with anemia have also aPL, and these autoantibodies probably are involved in red blood cells destruction in lupus and APS. The minority of patients have both thrombocytopenia and anemia (Evan’s syndrome), which can be detected in about 5% of lupus patients and 10% of the patients with primary APS. Other cases characterized by anemia might be life-threatening due to anemia caused by cell breakage in thrombosed small vessels. These severe conditions are characterized by multiple small vessel thrombosis. Thrombotic thrombocytopenic purpura (TTP) consists of thrombocytopenia, brain injury, and anemia with red blood cells with distorted shape, whereas hemolytic-uremic syndrome (HUS) which affects usually children is associated with kidney rather than brain injury. TTP occurs in the minority of patients with lupus and with primary APS, and there is a possible association between aPL and this manifestation. It is not proved but is likely that these autoantibodies contribute to the pathogenesis of TTP in lupus and primary APS. aPL have been in a significant proportion of HUS patients as well. A similar syndrome is HELLP (hemolysis, elevated liver enzymes, low-platelet count) which includes these manifestations and usually affects women during pregnancy. It is unclear whether aPL are associated with HELLP, but in study they have been detected in 70% of women with HELLP.

**Leukopenia.** This term implicates low levels of white blood cells. Leukopenia is much more frequent in lupus and secondary APS than in primary APS patients. Anti-cardiolipin autoantibody of the IgM isotype might be involved in the pathogenesis of leukopenia in these patients.

**Renal Injury in APS**

The kidneys are a target affected in many systemic diseases such as diabetes mellitus, hypertension, and also in SLE. As there is a pro-coagulant state in APS, renal artery thrombosis can also occur in APS, emboli blocking the renal artery, or alternatively severe arterial stenosis. Disruption of renal blood flow of any reason leads to hypertension, and occasionally to severe and life-threatening
hypertension. Restoration of renal artery blood flow by catheterization of the affected artery can improve renal function and blood pressure control as well. In some cases the first and sole manifestation of APS involves the kidneys, and in several cases of uncontrolled hypertension, antiphospholipid antibodies and renal artery stenosis have been found. Renal vein thrombosis can also be part of APS clinical manifestations, and the tendency to this thrombosis occurs mainly in the presence of nephrotic syndrome (excretion of large amount of protein in the urine). Even though most of these cases have been reported among SLE patients, those patients having lupus anti-coagulant have increased risk for renal vein thrombosis. Some of these vessels thrombosis can lead to renal infarction, death of some part of the kidney tissue with the subsequent impairment of renal function and induction of secondary hypertension. Emboli from the heart can also cause renal infarction. Thrombosis might also occur within the small vessels of the kidneys, including arterioles and venules and even the glomerular vessels through which the serum is infiltrated. Unfortunately, in severe cases when renal transplantation is indicated following chronic renal failure, the presence of antiphospholipid antibodies is associated with increased chance of transplant rejection and thrombosis in the transplanted kidney.

**Abdominal Organs Affected in APS**

The spleen include many cells of the immune system named lymphocytes, whose primary role is to fight infectious agents. Splenic infarction has been described in APS patients, as well as shrinkage of the spleen following small but persistent thrombotic events leading eventually to dysfunction of the spleen. The pancreas have a central role in secretion of hormones into the bloodstream such as insulin, and it also have an important role in food digestion due to secretion of enzymes which digest fat. Pancreatitis (inflammation of the pancreas) has been described only few times in APS patients. The clinical manifestations of pancreatitis are central or left-sided abdominal pain. However, intestinal manifestations of APS are by far more frequent. Thrombosis of the intestinal arteries can result in intestinal necrosis manifested by sudden severe abdominal pain with abdominal distension. An earlier pathology is abdominal angina resulting from narrowing and incomplete occlusion of the intestinal arteries. The clinical manifestations in the latter case include post-prandial abdominal pain, as meals induce increase in intestinal blood flow, which is limited in the narrowed vessels. Therefore, the pain which results from decrease in intestinal blood flow develops.
The liver has many important functions in the human body including proteins and fat production, and neutralization of various toxins. The liver can be affected in APS in various forms, although these manifestations in general are not frequent among APS patients. **Budd-chiari syndrome** results from interference of hepatic venous drainage. Liver venous thrombosis can be accompanied by thrombosis of larger veins such as the inferior vena cava which drains the blood to the heart. Budd-chiari syndrome can be acute or chronic, lead to death due hepatic failure, or alternatively can completely resolve. Disruption of blood flow is possible also within the liver, and similar to many other organs, liver infarction has also been described. aPL have been found in many patients having liver cirrhosis (a chronic disease manifested by dysfunction of the liver), portal vein hypertension, and among patients having hepatitis C virus. In these cases, the presence of autoantibodies was not associated with the frequent clinical manifestation of APS, as these patients usually did not develop thrombosis and infarctions.

**Hearing Impairment in APS**

Hearing loss can be caused due to impairment of blood supply to the cochlear nerve, and aPL might affect thrombosis in these small vessels. Indeed, these autoantibodies have been detected in some of the patients having sudden hearing loss, in a varying frequency from very low to even about quarter of the cases. The most frequent autoantibody was aCL. Sudden hearing loss also occurs in increased frequency in other autoimmune diseases such as lupus or Sjogren's syndrome, but even in these diseases it is associated with the presence of aPL.

**APS and the Eyes**

Eyes involvement in APS is relatively frequent, and can be found in most patients. Usually both eyes are involved, due to injury to the central nervous system. However, one eye involvement also occurs in APS, and the underlying mechanism in the latter case is decreased blood supply to the eye or an inflammatory reaction. Eye manifestations can be found in 88% of APS patients, but it is less frequent in patients taking anti-coagulants. The specific manifestations of APS involving the eyes include anterior chamber injury including scleritis, conjunctival aneurisms, keratitis, and damage to the pupil. The posterior chamber of the eye can also be involved in injury to the retina, the part of the eye responsible for transmitting vision to the brain. Damage to the retina reflects inflammation or obstruction of blood flow in retinal vessels. Retinal detachment which may evolve can end up in blindness. Another pattern of visual injury is the result of injury to the cranial nerves which supply eyeball muscles, or injury to the optic nerve itself.
The symptoms presented by patients having eye manifestations of APS are diverse and can include double vision, ocular pain, headache, visual fields impairment, transient visual loss in one or both eyes. Some of these symptoms were associated with the presence of aCL.

**The Endocrine System Involvement in APS**

The endocrine system is composed of several glands whose role is secretion of various hormones having crucial roles in maintenance of normal function of the human body. Several cases of dysfunction of these glands have been described in APS. These include decreased function of the pituitary gland (hypopituitarism), hyperparathyroidism (increased secretion of the parathyroid hormone which affects the calcium balance), and hyper- or hypothyroidism. In addition, in the minority of diabetes mellitus patients who have insulin deficiency or insulin resistance, aPL have been detected, and in some of these cases an association was found between autoantibodies presence and the vascular complications of the disease. Nonetheless, the adrenal is the endocrine organ most commonly affected in APS. The adrenal produces male steroids, corticosteroids, and aldosterone which affects salt balance in the kidneys. It is usually affected in APS by impairment of blood supply (Figure 30). Occasionally adrenal injury forms part or the beginning of catastrophic APS.

**Bones and Joints in APS**

Bones, muscles and joints are usually not affected in patients having APS. However, as APS is frequently secondary to other autoimmune diseases, including lupus, these diseases themselves can have manifestations affecting the joints, such as arthritis. Whereas primary APS is not characterized by arthritis, arthralgias...
(without inflammation manifested as swelling, redness and joint dysfunction) are relatively common in APS. In addition, bone marrow necrosis has also been reported in few patients having APS. This manifestation of APS results from hyper-coagulability and leads to severe impairment in blood cells production, manifested by anemia, thrombocytopenia and leukopenia.

The main injury to the bones in APS is avascular necrosis, which results from blood supply impairment. The most characteristic sites of injury are femoral heads, other parts of the femoral bone, tibia, humerus, wrist and foot bones. The minority of patients are affected, about less than 5%, but this injury is much more prevalent in lupus patients treated with steroids who also have secondary APS. Occasionally avascular necrosis is detected only in imaging studies of the bones and is not accompanied with symptoms, whilst in other cases it can cause bone or joint pain in the affected region.
Chapter 3: Treatment of APS

Treatment of Thrombosis

Treatment of thrombosis in APS is determined based on several factors: overall patient's condition, type of thrombosis, and the affected organs. For example, thrombosis in a coronary artery which supplies blood to the heart can be treated early by catheterization of the occluded vessel, turning it into patent and supporting it with intra-arterial stent. Such treatment can prevent myocardial infarction and necrosis, save patients' life or avoid functional disability. Once for one reason or another this catheterization is not an option, treatment for a patient with myocardial infarction includes aspirin and heparin. Aspirin is an anti-inflammatory and analgesic drug which also has a preventive and therapeutic effect on blood coagulation. Aspirin decreases the ability of blood platelets to form blood clots, and thus the blood turns into less 'sticky' (aspirin does not 'dilute' the blood, as generally said by mistake). During the first few hours following coronary artery occlusion, aspirin administration by chewing may decrease blood clot area and also assist in the spontaneous disappearance of the thrombus. Heparin is an anti-coagulant which acts in another mechanism of action: it directly inhibits one of the coagulation factors that promotes formation of blood clots. Heparin is given intravenously, but a similar drug called low-molecular weight heparin (LMWH) can be given in subcutaneous injections.

Treatment of deep venous thrombosis (such as in thrombosis of the thigh veins) includes heparin or LMWH administered for at least five days. Treatment goal is prevention of blood clot increase, and enhancement of spontaneous disappearance of the blood clot. This is also the treatment in cases of deep venous thrombosis complicated by pulmonary emboli. In the minority of cases, once patient’s condition is severe due to large pulmonary emboli or recurrent emboli, other therapeutic interventions are possible such as insertion of an 'umbrella' into the inferior vena cava that should catch the blood clots before they reach the lung, infusion of thrombolytic agent (a drug that actively dissolves the blood clot), and even surgery in order to remove big blood clots in the pulmonary arteries. In most cases, heparin is sufficient, but since it should be given only intravenously, an alternative anti-coagulant drug can be taken orally: warfarin (Coumadin). The anti-coagulation never starts with coumadin therapy, as several days are required in order to express the anti-coagulant activity of coumadin, and therefore heparin treatment continues in parallel with the beginning of coumadin therapy until there is a proof in the laboratory tests that coumadin already
expresses its anti-coagulation properties. Coumadin dosage differs from patient to another, but its anti-coagulant effect depends on a value named INR (international normalized ratio) which can be measured by blood test. A patient who is not treated with anti-coagulants have an INR level of approximately 1.0. The optimal INR for APS patients having venous thrombosis is around 2.5, and actually between 2.0 and 3.0. The presence of this INR level signifies a tendency of blood coagulation two or three times less than without treatment with coumadin. In this stage, heparin therapy can be stopped. Coumadin treatment can result in adverse effects, as while it antagonizes coagulation, it also posses the patient at risk for bleeding, including life-threatening bleeding. Coumadin therapy necessitates careful monitoring of INR levels in that range, as higher INR levels are not more effective, while they are associated with increase in bleeding cases.

The swelling of the thigh and intra-venous thrombus usually disappear following few days of treatment. However, aPL increase the chances to form further blood clots. Therefore, coumadin therapy should be continued for longer periods in order to prevent or significantly decrease the chances of recurrent thrombosis. In general, long-term coumadin treatment significantly decreases chances of recurrent thrombosis, and the longer the treatment is, the smaller the recurrence rate of thrombosis after the end of coumadin treatment. The physician should determine the duration of coumadin treatment and therapy policy in general. After a first event of deep venous thrombosis it is possible to treat the patient with coumadin for six months combined with monitoring of other risk factors for thrombosis such as smoking, hypercholesterolemia, obesity, and lack of physical activity. Thrombosis recurrence after the end of weeks to months coumadin therapy, or alternatively recurrence of thrombosis while under treatment, would necessitate administration of coumadin for years, maybe for good. In case of coumadin failure in prevention of recurrent thrombosis, it is possible to increase coumadin dosage in order to achieve a higher INR level, or to add other anti-coagulants which affects platelets. The treatment in this complexed cases would be determined by the physician and would be adjusted specifically in every case.

I had deep venous thrombosis of the thigh and I am treated with coumadin. I am not worried regarding another episode of thrombosis, as apart from swelling and a little pain it was not so disturbing. However, coumadin therapy is inconvenient; should I stop it?

Absolutely not! Cessation of coumadin treatment is associated with significant chances of recurrent thrombosis not only in the location of the primary thrombus, but in any other vessel as well, so that you may have pulmonary emboli,
myocardial infarction and stroke. You must not stop coumadin therapy without consulting your physician, as the results can be disastrous.

Aspirin treatment following cases of strokes (CVA or TIA) is given in order to prevent additional strokes. The aspirin dosage is 75–325 mg daily. Stroke recurrence rates among patients having aPL are not significantly different compared with patients without these autoantibodies, and in addition coumadin therapy is not superior to aspirin. If the stroke is associated with severe stenosis of the carotid arteries which supply the brain, a surgery is indicated in order to remove the atherosclerotic plaque which narrows the arterial lumen.

The treatment of deep venous thrombosis in other sites (e.g. veins of the arms) is similar to treatment of deep venous thrombosis of the thighs. The management of arterial thrombosis depends on arterial type. In cases of intestinal thrombosis a surgery might be necessary in order to remove necrotized part of the intestine, and in cases of renal artery thrombosis catheterization can be used in order to reopen the occluded artery.

**Treatment of Recurrent Pregnancy Loss**

The chance of pregnancy loss among women having recurrent pregnancy loss as a manifestation of APS is as high as 85%–90%. The approach to treatment of recurrent abortions in APS included therapy aimed at suppression of aPL production, and treatment with anti-coagulants against the pro-coagulant effect of aPL that induce blood clots in the placenta. Steroids can suppress autoantibody production, and they are a leading therapy in many autoimmune diseases. However, steroids are generally not used for treatment of pregnancy complications in APS, as their efficacy is lower than the alternatives, and they also carry associated adverse effects. Treatment with intravenous immunoglobulin (antibodies which neutralize or decrease production of aPL) is helpful in some of the cases, but it is not more effective than anti-coagulation. There is a small sub-group of women in which intravenous immunoglobulin therapy have additive effect to that of anti-coagulants. **The regular treatment of recurrent pregnancy loss in APS is with aspirin and heparin**, usually in a combination of both. Both drugs antagonize coagulation, and aspirin also have a beneficial effect on placental blood flow. There is controversy regarding the need to add heparin to aspirin therapy. Most researchers support an additive role of heparin combined with low-dose aspirin, as the combination of both drugs beginning with pregnancy confirmation leads to a high rate of live birth rates: around 80%.
Infertility, *in vitro* fertilization need and embryo transfer failure have been suggested as possible manifestations of APS, but they are usually not included in the syndrome and do not mandate anti-coagulation therapy. Women having APS which undergo *in vitro* fertilization might be in increased risk of thrombosis due to the high levels of estrogens they are exposed to during ovulation induction. In addition, women treated with anti-coagulant due to previous thrombosis are at risk for bleeding following egg retrieval. In these cases it is recommended to treat the patients during *in vitro* fertilization cycles with heparin rather than coumadin, to stop heparin therapy few hours before egg retrieval, and restores heparin administration several hours after the procedure.

**Additional Therapeutic Options**

Occurrence of thrombosis in APS is the result of aPL presence, but other factors contribute in some of the patients to atherosclerosis acceleration and thrombosis. Therefore, in addition to anti-coagulation therapy, an additional effort should be undertaken in order to minimize the risk for blood clots formation. This can be done by weight reduction, regular physical activity, smoking cessation, correction of hypercholesterolemia by diet or drugs, treatment of diabetes, oral contraceptives redrawing, correction of blood homocysteine levels by treatment with folic acid, and blood pressure control.

I was diagnosed with APS due to recurrent miscarriages. Should I also stop smoking?

Definitely yes! Your recurrent abortions as the only manifestation of APS are usually the result of thrombosis and placental injury, but the very same aPL increase the chance for thrombosis in every vessel. Smoking increases the risk for thrombosis and therefore it should be stopped.

There are several other therapies which are usually not in use, i.e. most patients and most clinical manifestations do not require their use. However, in some cases these therapies can be given:

**Intravenous immunoglobulin (IVIg).** This drug is composed of antibodies from the blood of thousands of donors. IVIg is helpful in the treatment of many autoimmune diseases, including immune thrombocytopenic purpura. IVIg use in APS is relatively rare, both due to its high cost (about 3,000$ for a single treatment course, usually six courses are needed), and the efficacy of the anti-coagulants. In special circumstances when other effects of aPL in addition to pro-coagulant activity are requested, such as thrombocytopenia, it is possible to use IVIg.
**Immunosuppressive agents.** These drugs including cyclophosphamide, methotrexate, azathioprine and others are given as a treatment in many autoimmune diseases such as lupus and rheumatoid arthritis. They are not used in most cases of APS, but in rare cases of APS they might have a therapeutic role, as in myelitis. These drugs are also used for treatment of patients having lupus and secondary APS.

**Anti-malaria.** The drug hydroxychloroquine (plaquenil) is given to lupus patients, mainly those having skin involvement. It has mild anti-coagulant activity, and hence might aid to further decrease thrombosis occurrence among APS patients.

**Future and Experimental Therapies**

In addition to the currently used treatment of APS, the great research undertaken in this field provide hope for development of additional therapies in the future that would increase the rate of patients enjoying a successful treatment, and prevent thrombosis and miscarriages. In addition to IVlg treatment, specific therapy with antibodies against aPL was also found successful. The same is true with respect to antibodies to CD4, a molecule present on lymphocytes (cells of the immune system). Other experimental therapies include immunization with DNA molecules, use of parts of β2GPI molecule, induction of tolerance to APS by oral feeding with β2GPI, and administration of bromocriptine (which controls prolactin levels) and interleukin-3 (one of the substances which controls the communication among immune system cells).
Chapter 4: The Autoantibodies in APS

APS is characterized by several autoantibodies, which are included in the aPL group. Even though aCL and LAC are the only autoantibodies which are used as criteria for the diagnosis of APS, other autoantibodies can also be detected in patients’ plasma, and these also have clear relationship with the clinical manifestations of APS (Figure 31). The primary tests for diagnosis of APS include aCL and LAC, but if these autoantibodies cannot be found but yet the clinical picture is highly suggestive of APS, other autoantibodies should be searched for, such as anti-β2GPI and other aPL.

![Antiphospholipid Antibodies](chart.png)

**Figure 31.** Distribution of various autoantibodies in over 500 APS patients. IgG anti-cardiolipin is the most important diagnostic autoantibody which was found in 297 patients. The second most frequent autoantibody is lupus anti-coagulant. The co-occurrence of both lupus anti-coagulant and anti-cardiolipin increases tremendously the chances for blood coagulation, and this finding affects accordingly the therapeutic approach. Nonetheless, the distribution of autoantibodies suggests that even if a patient presents with typical clinical manifestations of APS but without lupus anti-coagulant or anti-cardiolipin antibody, the presence of other autoantibodies should be searched for such as IgM anti-cardiolipin, anti-beta-2-glycoprotein-I, or other antiphospholipid antibodies.
**Lupus Anti-Coagulant (LAC)**

The term LAC implies autoantibodies (of the IgG, IgM or both types) which can inhibit phospholipids-dependent coagulation tests *in vitro*. Usually there is a close relationship between laboratory tests and the real *in vivo* state, hence inhibited coagulation tests *in vitro* signifies decreased blood tendency to form clots. However, as opposed to other coagulation inhibitors, these autoantibodies surprisingly are associated with increased risk for coagulation and formation of thrombosis. LAC are found in APS but also in other autoimmune diseases, following administration of several drugs, after various infectious diseases including the minority of children who had pharyngitis.

**If the laboratory test demonstrates coagulation inhibition, why there is actually hyper-coagulability?**

The coagulation tests are phospholipids-dependent. Therefore, LAC which binds to phospholipids inhibit the laboratory tests, whereas within the body this binding to phospholipids promotes coagulation in various mechanisms.

**Anti-Cardiolipin Autoantibodies (aCL)**

aCL are the autoantibodies which are most frequently used for the diagnosis of APS. The association between aCL and the clinical manifestations of APS exists mainly in medium to high titers of the autoantibody which persist for long. The IgG isotype is the most frequent found, but IgM and IgA aCL autoantibodies can also be detected, and they also are associated with the clinical manifestations of APS. Since aCL is found in 80%–90% of patients having APS, it is a very sensitive test for diagnosis of the syndrome. Nevertheless, aCL is not a very specific test since it can be detected also in other autoimmune diseases, following administration of several drugs, and after infectious diseases. The presence of aCL in a patient’s plasma signifies an increased risk for venous thrombosis, arterial thrombosis and myocardial infarction.

**aCL was detected in high titer form a sample of my blood, but I did not have any manifestation of APS. Should I be treated with preventive anti-thrombotic therapy?**

Probably yes. Your physician should evaluate the risk and the advantages of preventive anti-thrombotic therapy (usually aspirin), and would decide whether to recommend on such treatment.
**Anti-β2-Glycoprotein-I (β2GPI) Antibodies**

β2GPI is a serum protein which binds to negatively charged molecules, including phospholipids (Figures 32, 33). aCL actually binds to β2GPI which is linked to cardiolipin. The linkage between β2GPI and cardiolipin exposes an hidden site over β2GPI, and the autoantibodies bind to this site (Figure 34). Actually a great part of LAC antibodies are also directed to β2GPI. The presence of anti-β2GPI autoantibodies implies an increased risk for thrombosis, including myocardial infarctions in men, arterial and venous thrombosis in lupus patients, and in some of the studies, recurrent abortions. Anti-β2GPI autoantibodies are found in 40%–90% of APS patients.

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**Figure 32.** The protein beta-2-glycoprotein-I was completely investigated, it is composed of 512 amino acids. Its structure reminded researchers from the group of Takao Koike from Japan the structure of sushi, and thus it is named having sushi domains. Beta-2-glycoprotein-I is composed of 4 identical parts and an additional fifth part which binds cardiolipin.

**Figure 33.** Beta-2-glycoprotein-I is a protein which has a role in coagulation and atherosclerosis, as he protects against both. Upon appearance of autoantibodies directed against this protein in APS, its functions are impaired and this is one of the explanations for the enhanced atherosclerosis and hyper-coagulable state in APS. This figure is taken from the car plate of Dr. Robert Roubey, one of the leading investigators in the field.

**Figure 34.** A figure representing the association between anti-cardiolipin antibodies and beta-2-glycoprotein-I. Upon binding of both, an hidden site is exposed on the surface of the latter, making the affinity of anti-cardiolipin antibodies binding much higher.
Other Antiphospholipid Antibodies

aCL occasionally react with other phospholipids such as phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerol, and phosphatidic acid. Testing of this autoantibodies is not helpful usually in the diagnosis of APS; however, in some cases where aCL and LAC are absent, whereas the clinical manifestations are highly suggestive of APS, these autoantibodies can be detected and thus may be useful for the diagnosis of APS. For example, in about 10% of women having recurrent abortions do not have aCL, but yet they have elevated levels of one of those other aPL. Anti-phosphatidylethanolamine was found in one study in about half of lupus patients, and in third of them was the only aPL detected; yet these patients had the clinical manifestations of APS.

Other Autoantibodies Associated with APS

In some of APS patients, other autoantibodies which are also related to clinical manifestations can be detected. Anti-annexin-V antibodies are found in increased prevalence among women having recurrent pregnancy loss, and also in women having aPL. Annexin-V is found over placental cells, and it is possible that anti-annexin-V antibodies interferes with its anti-coagulant activity, thus promoting hypercoagulability in the placenta, impaired blood supply to the fetus and pregnancy loss.

Other autoantibodies are directed to the coagulation factor prothrombin. There is a weak association between anti-prothrombin autoantibodies and thrombosis. In about half of the studies dealing with this autoantibody, its presence was found associated with risk for arterial and venous thrombosis. Anti-prothrombin occasionally have properties of LAC, i.e. it inhibits coagulation in vitro.

Another autoantibody related to APS is anti-oxidized, low-density lipoprotein (LDL) autoantibody. LDL is the ‘bad’ cholesterol, as elevated levels of LDL are associated with atherosclerosis and cardiovascular diseases. Upon oxidation of LDL, it tends to accumulate within foam cells that reside in vessels walls. Anti-oxidized LDL antibodies are associated with enhanced atherosclerosis, and its presence in men predicted the occurrence of myocardial infarction several years later. There is a cross-reaction between aCL and anti-oxidized LDL antibodies, i.e. some of aCL antibodies bind to oxidized LDL, and therefore anti-oxidized LDL is considered as one of aPL.
How Do the Autoantibodies Act?

In some autoimmune diseases, the presence of autoantibodies signifies the presence of disease, but not necessarily the role of autoantibodies in disease induction (a pathogenic role, which causes the disease). It may also be so in APS, but there is a large sum of data which support the role of aPL in the induction of the clinical manifestations of APS. The production of aPL in animals, or alternatively injection of aPL to animals can induce the typical manifestations of APS: pregnancy loss, placental injury, thrombocytopenia, arterial thrombosis, and behavioral changes. aPL have a direct effect on brain tissue and fetal development. Nevertheless, most of the mechanisms of action of aPL are associated with pro-coagulant activity induced by the autoantibodies (Figure 35). This pro-coagulant tendency results form activation of endothelial cells which line...
the interior of vessels thus promoting to formation of blood clots, activation of platelets which form the primary thrombus (Figure 36), promotion of coagulation rate in plasma which takes place with phospholipids, and inhibition of natural anticoagulants.

**Does a high titer of aPL imply a higher risk for thrombosis?**
No. Currently there is no evidence to suggest that high titer of aPL can promote coagulation more than medium titer of these autoantibodies. Both titers imply an increased risk for thrombosis.

*Figure 36. One of the mechanisms for hyper-coagulability in APS. Upper plate- blood platelets incubated with irrelevant antibody move within the blood vessel. Upon exposure to anti-cardiolipin antibody, the platelets undergo aggregation, and form larger parts, which is the first stage of coagulation. This is only one of many mechanisms of action for explanation of the hyper-coagulability state in APS (the figure is in courtesy of Dr. Ricard Cervera from Spain).*
Chapter 5: Other conditions in APS

**Catastrophic APS**

As suggested by its name, catastrophic APS stands for some patients having severe manifestations of APS and severe disease course. This state is uncommon, and is characterized by disseminated coagulation which affects small vessels that supply blood to many organs. Most patients who had catastrophic APS were primary APS patients, or patients having lupus and secondary APS. In about two thirds of the documented cases, a factor which could have caused this syndrome was identified. This factor was usually infection, or less frequently surgery, trauma, redrawal of anti-coagulant therapy, use of oral contraceptives, and lupus flares (Figure 37). Occasionally two or more of these factors have been reported before occurrence of catastrophic APS, but in other patients no such inciting agent for APS could be identified. The clinical manifestations include a combination of skin, central nervous system, cardiac, pulmonary, renal, hematologic and gastrointestinal manifestations. Treatment consists of administration of several drugs and should not be delayed since the mortality rate in catastrophic APS is around 50%. The treatment includes intravenous anti-coagulation (heparin), steroids, intravenous immunoglobulin (IVIg), plasmapheresis, and immunosuppressive agents. Catastrophic APS is relatively uncommon, as only about 130 cases have been reported.

**Catastrophic APS Precipitating Factors (130 Patients)**

1. **Infections** - 36%
2. **Trauma** - 14%
3. **Cancer** - 9%
4. **Withdrawal of anticoagulants** - 7%
5. **Obstetric complications** (post fetal loss) - 5%
6. **SLE flares** - 2.5%
7. **Exposure to estrogen** - 2.5%

*Figure 37.* Several factors have been found as potential inducers of catastrophic APS in a work including 130 patients. The most frequent was infection (36%), followed by trauma, cancer, redrawal of anti-coagulants use, post-abortion state, administration of oral contraceptives, and lupus flare.
**Hypoprothrombinemia**

The concomitant presence of LAC which promotes coagulation, and low levels of prothrombin (hypoprothrombinemia) which is a coagulation factor, leading to hemorrhage, is relatively a rare manifestation of APS. The autoantibody usually leads to neutralization of prothrombin, and therefore an unusual hemorrhage develops. In these cases the preferred treatment is not with anti-coagulants, but rather with steroids that would depress autoantibody production. This therapy does not affect the hypercoagulability induced by LAC.

**APS in Children**

The prevalence of aPL among healthy children is 5%–10%. Among children with lupus, LAC can be detected in 22%, and aCL in 45%, similar to the prevalence of these autoantibodies in adult lupus patients. The clinical picture of APS in children includes mainly deep vein thrombosis, like thrombosis of deep veins of the lower extremities. aPL were also found in most children who had strokes of unknown etiology. Other clinical manifestations include seizures, budd-chiari syndrome which is characterized by disruption of drainage of venous blood from the liver (APS is the main cause of this syndrome in children), and thrombosis in various arteries and veins (Figure 38). Thrombocytopenia is also frequent in APS, as opposed to myocardial infarction of heart valve vegetations. Mostly, children having APS are older than 12 years of age. The expression of APS in children, which is an acquired hyper-coagulability state, is related also to inherited hyper-coagulability states. Indeed the combination of inherited hyper-coagulability state and presence of aPL contribute to formation of thrombosis in children. A special form of APS in children is a rare manifestation following varicella infection (chickenpox): autoantibodies directed to the natural anti-coagulant ‘protein S’ occur together with aPL, resulting in thrombosis.

**Figure 38.** APS in children.
The picture is of a child with a butterfly rash which is typical for lupus, and thrombosis which caused gangrene in the distal tip of the toe.
Newborns might also be affected by APS, but this mainly due to pre-term birth and pre-eclampsia which occur in some of pregnant APS patients. As opposed to lupus, in which there is a clear subgroup of newborns which are affected by lupus which is transferred by specific autoantibodies (anti-Ro), maternal-fetal transfer of APS is possible but is extremely rare (Figure 39). Several cases of thrombosis in newborns to mothers having APS have been described, usually thrombosis in the arteries supplying the brain.

I am pregnant and having APS. What are the chances of my child to be also affected by APS?

Adequate treatment during pregnancy would prevent premature birth complications in most cases, and newborn injury as a result. The risk for genetic transfer of APS is very low, even though it is higher compared with family who do not have APS. There is an extremely low risk for autoantibody transfer through the placenta, and induction of thrombosis in the newborn. In these cases the aPL tend to disappear within several weeks and hence do not further risk the newborn.

Atherosclerosis and Antiphospholipid Antibodies

Atherosclerosis is a pathological process characterized by fat accumulation in vessels walls and gradual narrowing of the arteries. In most cases of myocardial infarctions and strokes, there is severe atherosclerosis in the coronary and carotid arteries, respectively. aPL enhance thrombosis, but they might also enhance atherosclerosis and thus further enhance arterial thrombosis. Animal studies demonstrate that aCL and anti-β2GPI autoantibodies enhance atherosclerosis. In addition, these autoantibodies and also anti-oxidized LDL antibodies are found in increased prevalence and in higher levels in patients having clinical manifestations of cardiovascular diseases, and occasionally before appearance the clinical manifestation (for example: carotid artery stenosis as measured by ultrasound, coronary artery stenosis).
I have lupus but I do not have aPL. Am I at decreased risk for atherosclerosis development?

No. Cardiovascular diseases are more prevalent among lupus patients compared with the general population due to several factors. aPL represent only one factor capable of augmenting atherosclerosis in lupus patients. Therefore, lupus patients should control risk factors for cardiovascular diseases such as smoking, high plasma cholesterol levels, diabetes mellitus, hypertension, and regular exercise.

**Seronegative APS**

There are few cases in which the clinical picture is highly suggestive for the presence of APS, whilst the laboratory tests fail to detect LAC or aCL. These cases could be APS with other aPL which are not included in the criteria for diagnosis of definite APS: IgA isotype of aCL, other aPL, false positive test for syphilis, or anti-mitochondrial antibodies. It is also possible that during the acute event of thrombosis, aPL cannot be detected since they are consumed into the blood clot. Repeated measurement of these autoantibodies several weeks later could help and detect them. It is also possible that these cases represent other hyper-coagulable states, like hereditary ones.
The term prognosis implies the ability to predict disease course, life expectancy and future quality of life. Among lupus patients, there is increased mortality rate among patients having secondary APS compared with lupus patients who do not have APS, mainly among patients who had thrombocytopenia and arterial thrombosis, but also in patients who had venous thrombosis and hemolytic anemia. The concomitant presence of APS and lupus can aggravate renal injury, and lead also to permanent brain damage. The estimation of prognosis among primary APS patients is more difficult. Among patients who had recurrent pregnancy loss, aspirin and heparin therapy significantly improves live birth rates. The 10-year mortality in primary APS is estimated in 10%. Involvement of the different body systems in APS can lead also to functional impairment.
Published Articles on APS by Professor Yehuda Shoenfeld


