As a mother of a diabetic child recently pointed out, young people with diabetes are more concerned about losing their driving licences (as a result of severe hypoglycaemia) than the risk of renal failure later. We may therefore be overestimating the impact of the diabetes control and complications trial on our patients' acceptance of stricter control. Certainly we need to pursue better methods of applying good glycaemic control in our diabetic patients and other ways of preventing chronic complications. In the meantime, increased expertise achieves lower rates of severe hypoglycaemia.[8-10]

Undoubtedly, improved glycaemic control is one way of preventing the chronic microvascular complications of diabetes mellitus. The diabetes control and complications trial suggests—at least for retinopathy—that the lower the glycated haemoglobin concentration the lower the risk. So any improvement in diabetic control is worth while and each patient should be helped to achieve the best possible control. But the inverse relation between glycated haemoglobin concentration and risk of severe hypoglycaemia was also a continuum. Patients will need to choose for themselves between the effort and risk of intensified metabolic control and the risks of later microvascular complications. Those who care for them need to be able to help them apply their choice with least harm. The diabetes control and complications trial offers a firm base on which to make those choices.

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Routine measurement of fibrinogen concentration

Not clinically feasible

The concentration of plasma fibrinogen is a strong independent risk factor for the development of arterial thrombotic disorders.[1,2] Several carefully designed epidemiological studies have identified fibrinogen as a major risk factor for myocardial infarction,[3,4] and positive associations with raised fibrinogen concentrations have also been reported for thrombotic stroke, transient ischaemic attacks, peripheral arterial disease, diabetic vascular conditions, angina pectoris, and chronic bacterial infection.

Quantifying other independent risk factors for cardiovascular disease (for example, hypercholesterolaemia, hypertension, and smoking) is relatively easy, but accurate measurement of fibrinogen concentration is neither widely available nor frequently requested as part of general screening programmes in Britain. Should it be? Is measuring fibrinogen concentration a practical, useful, and cost effective laboratory investigation that should be included in future screening programmes?

Several problems, relating both to the fibrinogen assay and to biological variation, need to be considered. Unlike most other haematological variables, fibrinogen must be measured in plasma. It is unstable on storage, and ideally fresh anticoagulated plasma should be analysed. In the Clauss assay, the commonest technique used in routine laboratories, various dilutions of a standard plasma with known fibrinogen concentration and dilute test plasma are clotted with excess thrombin.[5] The fibrinogen concentration is proportional to the clotting time, which allows the concentration to be quantified. Heparin, fibrinogen degradation products, and abnormal forms of fibrinogen can, however, interfere with the assay.

Most British haematology laboratories have introduced some form of automated coagulometer, which can perform such assays or produce a "derived fibrinogen" value from the prothrombin time test.[6] The test may be calibrated by testing a standard plasma of known fibrinogen concentration with each new batch of prothrombin time reagent; however, lipaemia affects the reliability of derived values.[7] Standardisation is also difficult given the instability of reference materials during lyophilisation and the lack of national and international standard preparations. Although fibrinogen assays are relatively simple, the coefficient of variation from national quality control surveys with more than 350 laboratories participating has ranged from 15% to 20%. This raises the question of the usefulness of a single fibrinogen determination in individual patients at risk of or who have developed a specific clinical thrombotic condition.

Not only are there technical problems with the assay but fibrinogen concentrations are subject to considerable biological variation. Fibrinogen is one of the major acute phase reactant proteins, and increased hepatic synthesis occurs as a physiological response to inflammation and tissue necrosis.[8] Altered protein catabolism due to intravascular consumption may also influence circulating plasma concentrations. The plasma fibrinogen concentration rises with age, and a considerable gender difference exists.[9] The concentration is increased in users of the combined oral contraceptive[10] and increases during pregnancy.[11] A rise also occurs after the menopause; the effects of hormone replacement therapy are inconsistent.[12]

In well designed research many of these problems can be addressed by use of a single laboratory with specific dedicated equipment, staff, and in house procedures for quality control. But in a busy routine setting it is virtually impossible to control for these numerous variables and thus allow a meaningful clinical decision to be made on a single fibrinogen estimation.

The main therapeutic question is how to lower a raised fibrinogen concentration safely. Although specific defibrinating agents—such as ancrod—are available, they are not a viable clinical option. Secondary drug approaches with fibrates and other lipid lowering drugs, diet, and better diabetic

control may successfully lower fibrinogen concentration. But this still leaves a difficult question: given the many sources of variation, is a single measurement of fibrinogen concentration of any practical value?

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Antiphospholipid syndrome

A common cause of thrombosis

Ten years have elapsed since our original description of the anticardiolipin syndrome, comprising arterial and venous thrombosis, strokes, migraine, livedo reticularis, recurrent abortion, and occasional thrombocytopenia.[1] Other features of what is now widely known as the antiphospholipid syndrome are labile hypertension, chorea, epilepsy, amaurosis fugax, myelitis, early myocardial infarction, valvular heart disease, the Budd-Chiari syndrome, haemolytic anaemia, adrenal infarction, and Addison's disease.[2]

The anticardiolipin test, which has been internationally standardised,[3] has become a critical factor in identifying patients with the syndrome. Most patients with clinical thrombotic problems have persistent moderate to high titres of IgG antibodies to cardiolipin (a phospholipid). A few, however, have raised titres only of IgM antibodies.

The syndrome's overriding association is with thrombosis, both venous and arterial; its association with arterial thrombosis distinguishes it from many other hypercoagulation disorders. Vessels of all sizes may be affected, and the vascular pathological appearance has consistently been of bland occlusion without inflammatory infiltrate.[4] The antibodies themselves persist for many years, possibly a lifetime. Thus one of the key clinical questions is what additional factors lead to the sudden development of thrombosis.

Cerebral ischaemia is by far the most important neurological manifestation of the antiphospholipid syndrome.[5] Although the cerebral disease is likely to result from widespread thrombosis of small (and sometimes large) cerebral vessels, other mechanisms may contribute. In a prospective echocardiographic study of 132 patients with systemic lupus erythematosus valvular lesions were relatively common—more so in patients with antibodies to phospholipids.[6] Another study, designed to investigate the relation between antibodies to phospholipid and strokes, found that one third of patients who experienced strokes and had raised titres of antibodies to cardiolipin had abnormal echocardiograms.[7] In some patients untreated recurrent cerebral infarcts have led to multi-infarct dementia. Behavioural disorders, psychiatric disturbance, and epilepsy may well come to be recognised as an important feature of the syndrome, possibly hitherto underreported.[2]

The association between antibodies to cardiolipin and recurrent spontaneous abortion is one of the most consistent features of the syndrome. The rate of miscarriage in patients with antibodies to phospholipid is high.[8] The prevalence of the antibodies in women with recurrent spontaneous abortion may be as high as one in five,[9] and, increasingly, testing for the antibodies is becoming routine in women with recurrent miscarriages. The mechanism is thought to be a progressive thrombosis of the microvasculature of the placenta, and in pregnancies that go beyond mid-term a progressive fall off in fetal circulation can be shown with Doppler flow studies.[10]

Clinical experience suggests that among patients with raised antibody titres to phospholipid there are subsets with varying thrombotic risk. This concept is of key importance because it suggests that the current antibody assays detect a heterogeneous group of antibodies and only a particular subset is associated with the thrombotic syndrome.[11 12]

The mechanism of thrombosis is unknown. Recent studies have shown that a subset of antibodies to phospholipid reacts with the complex of phospholipid and the serum protein β_2 glycoprotein 1, the so called cofactor which inhibits factor XII activation, platelet activation, and prothrombinase activity.[13] Interference with these properties might provide a potent way in which antibodies to phospholipid could predispose to a prothrombotic diathesis.

The mechanism(s) responsible for the induction of antibodies to phospholipid remain an enigma. Recently, Gharavi and colleagues showed that, although pure phospholipids are not immunogenic, immunisation with purified β_2 glycoprotein 1 resulted in the production of antibodies to cardiolipin.[14] This work suggests that phospholipid binding protein may be the key immunogen.

The discovery of the antiphospholipid syndrome has provided new insights for treatment. Low dose aspirin (75 mg a day), possibly in addition to subcutaneous heparin in those with a history of thrombosis, is a logical first line of treatment and is improving the success rate in pregnant women who are positive for the antibody.[15 16] Little doubt now exists that patients with high titres of antibodies to phospholipid and previous major thromboses require long term, possibly lifelong anticoagulation, and in these patients international normalised ratios have to be kept around 3.[17] Steroids and immunosuppressive drugs to reduce antibody titres have not provided long term benefit.

The recognition that antibodies to phospholipid are associated with a distinct syndrome, including arterial and venous thrombosis, has opened up new avenues for treatment and research. Whether the pathogenetic effects of the antibodies are on platelets, endothelial cells, or clotting