Conference report

Third International Antiphospholipid Conference: barbecues, rum punches, and kaps

Sipping rum punches, tasting barbecued lobster, and idling by the pool in the tropical January moonlight of Kingston, Jamaica were only a few of the many highlights of the Third International Conference on Antiphospholipid (aPL) Antibodies. For most of the 120 participants from 22 countries 5–8 January 1988 will have been a memorable respite from the annual battle of winter, snow, and subzero temperatures. Despite the temptations of the poolside and friendly barmen, a surprisingly large audience attended all 10 sessions held in three days, during which over 100 abstracts were presented. On the third morning of the meeting over 80 participants devoted four hours of discussion to finalising plans for an international prospective study of patients with the 'antiphospholipid syndrome'—the study will be designated KAPS or (the Kingston antiphospholipid study).*

Each session of the conference was designed to reflect a current area of interest in antiphospholipid antibodies, and, compared with the two previous meetings in London (October 1984, April 1986), one sensed an increasing maturity in studies being performed to identify and manage affected patients prone to thrombosis and fetal loss. Several groups have started to look at mechanisms by which these antibodies may cause thrombosis, and others are exploring a variety of approaches to characterise the antibodies. Problems of standardisation of the lupus anticoagulant and anticardiolipin (aCL) antibody tests were exhaustively discussed, and it appears likely that there will at least be some agreement about the test methods to be adopted for including patients in the prospective study.

As had been the case in previous conferences a number of papers explored association of aCL antibodies or the lupus anticoagulant with thrombosis or fetal loss in patients with systemic lupus erythematosus (SLE). As has been noted in the recently published work, the data are confusing, probably because of variations in tests being per-

formed, measurement of level of positivity, and definition of patients with thrombosis. Many groups have started examining particular aspects of the thrombotic diathesis to which some patients with aPL antibodies are prone, in particular, cerebrovascular events. Although these patients present most frequently with cerebrovascular accident, Dr Levine (USA) found that other presentations included transient ischaemic attacks, visual disturbances (amaurosis fugax, ischaemic optic neuropathy, retinal artery or vein thrombosis), dementia, cerebral vein thrombosis, and death. A computed tomographic (CT) scan may show single or multiple infarcts, usually in frontal or parietal areas of the brain, and angiographic studies when positive usually show large vessel occlusion, but without evidence of vasculitis. Dr Gatenby (Australia) and Drs Gil and Khamashta (Spain and UK) identified some patients with aPL antibodies whose cerebrovascular events appeared to be secondary to emboli originating from heart valves affected by a marantic endocarditis. Two lupus anticoagulant positive patients, who were described by Dr. Gatenby, died after massive cerebral infarction, and a postmortem examination confirmed embolic cerebral infarction associated with marantic endocarditis. The association of aPL antibodies with a marantic endocarditis was suggested by Dr Lockshin and colleagues (USA) two years ago and has been noted by other groups since that time. Dr Englert (UK) studied the association of livedo reticularis with aCL antibodies and found that the relative risk of finding livedo in aCL positive patients compared with an SLE control population was 23:1. Cerebrovascular accident appeared to be more common in patients with livedo. As has been the case previously, no one found any specific treatment which consistently prevented recurrence of cerebrovascular events, but participants agreed that aspirin or oral anticoagulants, or both, appeared to be preferable to steroids.

Dr Harris (USA) and Dr Mackworth-Young (UK) reported 28 and 20 patients respectively, with features of the antiphospholipid syndrome. Both groups found that in affected patients *without* SLE

*Further details of the prospective study may be obtained from Dr E Nigel Harris, Department of Medicine, University of Louisville, Louisville, Kentucky 40292, USA.

joint symptoms, migraine, and thrombocytopenia were relatively frequent. An antinuclear antibody test was positive in 2/14 in one study (Harris) and in 10/19 in the other (Mackworth-Young). Both groups agreed that, in general, although many patients with the aPL syndrome did not fulfil accepted criteria for SLE, they had many of the clinical and serological features normally associated with SLE. The data presented by Alarcon-Segovia (Mexico) argued in favour of inclusion of thrombocytopenia as a criterion for the aPL syndrome as he had found thrombocytopenia with or without haemolytic anaemia to be strongly associated with aCL antibodies in a large series of patients with SLE.

There were several papers presented by obstetricians from North America and Europe on aPL related fetal loss. One study by Dr Branch and colleagues (USA) found that of 18 serum samples examined from women with severe pre-eclampsia occurring in the late second or third trimester of pregnancy, six had significantly raised aCL levels as well as positive lupus anticoagulant tests. Several groups reported data on treatment of women with aPL antibodies and recurrent miscarriages. Some groups reported that treatment with aspirin alone during pregnancy (Dr Tchobroutsky (France), Dr Derksen (Netherlands), Dr Lockshin (USA), Dr Elder (UK)), or aspirin and subcutaneous heparin (Dr Cowchock (USA)) were at least as effective as prednisone and aspirin. Other groups reported that even after suppression by prednisone of lupus anticoagulant activity and aCL levels (Dr Farquharson (UK), Dr Paul (Australia)) pregnancy outcome was often poor. Side effects noted frequently with prednisone treatment included diabetes, infection, and hypertension. Dr Scott (USA) reported an interesting patient with aPL antibodies who had two miscarriages despite treatment with prednisone and aspirin but who went on to have a live birth after paternal leucocyte immunisation and two five day courses of high dose intravenous immunoglobulin treatment. Despite criticism of the prednisone and aspirin treatment for women with aPL antibodies and fetal loss several groups (Dr Pattison (New Zealand), Dr Faden (Italy), Dr Carolis (Italy)) continue to find this treatment to be efficacious for women with recurrent miscarriages. All investigators agreed, however, that a planned randomised prospective trial of treatment of these women is necessary.

At a more basic level, studies of mechanisms by which aPL antibodies may cause thrombosis yielded more negative than positive information. Most groups pursued the Carreras and Vermeylen hypothesis, by which it is postulated that aPL antibodies inhibit prostacyclin production by endothelial cells.

Although several groups found that SLE sera had endothelial cell binding activity (Dr Meroni (Italy), Dr McCarty (USA), Dr Schorer (USA), Dr McCrae (USA)), there appeared to be little correlation with cardiolipin binding activity. Antiphospholipid antibodies appeared to have no effect on prostacyclin production by endothelium or on thromboxane production by platelets (Dr Derksen (Netherlands)). Dr Shorer and colleagues, however, found that both aPL positive sera and purified aPL antibodies inhibited thrombin stimulated production of prostacyclin by endothelial cells and thrombin stimulated production of thromboxane by platelets. Evidence of aPL antibodies influencing platelet function have yielded mainly negative results. Dr Casals (Spain) in a study of three patients with the lupus anticoagulant found no alteration in platelet number or turnover. Of note, however, were studies by Dr Khamashta (UK), Dr Rauch (Canada) using monoclonal aCL antibodies, and Dr Frampton (UK) who all found that these antibodies can bind freeze thawed or activated platelets. The functional significance of these latter observations requires further study. Drs Preston and Malia (UK) reported reduced free protein sulphur in patients with lupus anticoagulant activity. Several studies investigated the relation between the lupus anticoagulant activity and aCL antibodies measured by solid phase assay. It is becoming increasingly evident that each of these two groups of aPL antibodies are heterogeneous, perhaps with a variety of specificities. Although specificities of the lupus anticoagulant and aCL antibodies overlap, many observers have found some lack of concordance between the two tests.

The most tangible result of the conference, however, was the agreement by over 50 groups (some of whom did not attend the conference) to participate in a cooperative, international, prospective study of patients with aPL antibodies. One arm of the study will examine treatment of women with recurrent fetal loss and will conduct a prospective, randomised, controlled trial comparing prednisone plus aspirin with aspirin alone. A second proposed study will attempt to determine prospectively whether the rate of recurrence of venous thrombosis in patients with aPL antibodies is significantly greater than that of age, sex, and disease matched controls with venous thrombosis who do not have these antibodies. Both groups will be treated with oral anticoagulants for three to six months and treatment will then be stopped and the rate of recurrence of venous thrombosis determined in the two groups. A large number of patients will need to be recruited for the thrombosis study if meaningful results are to be obtained in a relatively short period of time (three to five years), but given current

interest world wide in this study, we may be able to recruit sufficient patients. It is likely, too, that a prospective study of aspirin treatment of patients with aPL antibodies and arterial thrombosis will be initiated.

For the above studies to start it is essential that a general agreement about the positivity of lupus anticoagulant and aCL tests is reached. Two committees (lupus anticoagulant and aCL) have been formed to establish criteria for positive tests and to start distribution of test samples to participating groups.

The strength of this conference was that it drew together the diverse specialties interested in aPL antibodies—rheumatologists, haematologists, obstetricians, neurologists, clinical immunologists, and membrane biochemists. Consideration of a single subject from so many angles helped us to learn more about the subject from our own particular perspective. Characteristics of the antiphospholipid syndrome may help us as rheumatologists to learn more about the pathogenesis of connective tissue dis-

orders; haematologists may learn more about cause of thrombosis in the absence of known risk factors; obstetricians may gain more insight into the problem of unexplained fetal loss; immunologists may understand more about this curious autoantibody which on binding an antigen exerts an in vitro prolongation of clotting tests. Most of us who attended this symposium believe that these conferences should continue, but we urge that aPL symposia like good wines should be tasted not too frequently lest they lose their appeal—a conference every 18 months to two years is probably quite enough.

Department of Medicine,
University of Louisville,
Louisville,
Kentucky 40292

E NIGEL HARRIS

Lupus Research Laboratory, GRAHAM R V HUGHES
The Rayne Institute,
St Thomas's Hospital,
London SE1