Across your desk come the notes of a patient just diagnosed with multiple sclerosis under your care. Pinned to the front is a laboratory report saying her antinuclear antibody (ANA) is positive. It is not clear why the test was done or who arranged it. Does that mean your patient has lupus? Or ‘lupoid sclerosis?’ Does it matter anyway? What should you do?

WHAT DOES A ‘POSITIVE ANA’ MEAN?
The traditional test of an antinuclear antibody is an indirect immunofluorescence test of the binding of serum to the nuclei of Hep-2 cells. The result is read as the greatest dilution at which binding to the cells is still visible; the greater the dilution (titre) the higher the concentration and/or affinity of the antibody. Some laboratories give the titre itself; others (trying to be helpful) report ‘positive,’ ‘strongly positive’ and so on. The pattern of binding (‘nucleolar’, ‘homogeneous’) is also sometimes described. A good laboratory will go on to test for antibodies to double-stranded DNA and ‘extractable nuclear antigens’ (Ro, La, Sm, Scl70, Jo-1, centromere and so on), all of which have their own particular significance; for our purposes only those associated with Sjogren’s syndrome are important (Ro and La).

Positive ANAs are found in ordinary people
A fairly standard definition of an abnormal ANA titre is 1 : 40, which has a prevalence in normal people of between 5 and 35%, usually higher in women. Of course, the prevalence of antibody positivity changes as the cursor shifts: 32% of normal adults were positive at 1 : 40 in one study, 13% at 1 : 80, 5% at 1 : 160 and only 3% at 1 : 320 (Craig et al. 1999). This means that, unless you are looking at an incredibly common disorder, a positive ANA at low titre is most likely to be a false-positive. Consider a review of 1010 consecutive ANA results at a teaching hospital (Slater et al. 1996): 15% of all patients, and 30% of those over the age of 65, had a titre of 1 : 40, but the vast majority of these patients did not have any rheumatological disease. If the cursor was raised so that only titres of 1 : 320 were considered significant, there were still more false (55%) than true (45%) positives for rheumatological disease.

Nowadays many laboratories have abandoned the traditional assay in favour of more convenient ELISA kits, which test the binding of patients’ sera to a cocktail of antigens that may or may not represent the full antigen profile of
Hep-2 cells. Although they give the impression of accuracy (an actual concentration of antibody is given), they are not an advance, at least not yet. For there are many different kits and little data on their validation. In one study of patients with lupus, of whom 88% had a positive ANA on the immunofluorescence assay, various ELISA kits reported positives in 62–90% (Emlen & O'Neill 1997). Antibodies to double stranded DNA are regarded as more specific for lupus but are less sensitive.

Multiple sclerosis is associated with an increased prevalence of autoantibodies

Most people accept that multiple sclerosis is an autoimmune disease. Like many other such diseases, the apparent specificity of the immune attack belies an underlying polyclonal increase in autoimmunity that does not usually find clinical expression. The relationship with thyroid autoimmunity is particularly illustrative. Thyroid disease is not a feature of untreated multiple sclerosis. However thyroid disease is increased amongst first-degree relatives of people with multiple sclerosis (Broadley et al. 2000), and can be induced in multiple sclerosis patients by immunotherapy (Coles et al. 1999; Durelli et al. 2001; Heesen et al. 2001). It is therefore no surprise that the prevalence of antithyroid antibodies is raised in multiple sclerosis (Ioppoli et al. 1990; Annunziata et al. 1999). Probably for the same pathogenic reasons, antibodies against smooth muscle and nuclear antigens are also found in higher frequency amongst multiple sclerosis patients compared to controls (Barned et al. 1995; De Keyser 1988). Indeed, in a large study, de Keyser found that multiple sclerosis patients were twice as likely to have detectable serum autoantibodies than healthy controls (41% vs. 23%).

WHAT COULD THE DIAGNOSIS BE?

So the odds are that your patient has regular multiple sclerosis and that the ANA result is spurious. But inaction is not justifiable. For there are real alternative diagnoses to be made with real consequences for the patient. By far and away the most important are the antiphospholipid syndrome and/or cerebral lupus. You should keep Sjogren's syndrome in mind and also there is that mysterious entity of lupoid sclerosis. On the other hand, it is unlikely that you are dealing with sarcoidosis or a primary vasculitic disorder such as Behçet's or Wegener's granulomatosis, because these usually do not generate a positive ANA.
Cerebral lupus

The wide range of estimates of the prevalence of CNS involvement (18–69%) in systemic lupus erythematosus (SLE) is probably due to the variable inclusion of depression and headache (Jennekens & Kater 2002). It is however, very unusual for SLE to present with a neurological syndrome, perhaps as few as 3% of all SLE presentations. Neurological involvement in SLE is a bad sign carrying a 5-year mortality of 45% (Scolding 1999). A non-evidence-based rule of thumb is that it is unusual to have full-blown SLE confined to just one system for any longer than 5 years; so an isolated neurological syndrome of longer duration is probably not due to SLE.

The standard diagnostic criteria for SLE (Table 1) nominate psychosis and seizures as defining neurological features of the disease. But a huge variety of neurological syndromes has been associated with lupus. Very helpfully, a recent systematic analysis has pruned this list down to 16 (Jennekens et al. 2002) (Table 2), most of which would not be mistaken for multiple sclerosis. The majority of these neurological syndromes are caused by cerebral ischaemia due to a small-vessel non-inflammatory proliferative vasculopathy characterized by hyalinization (Johnson & Richardson 1968; Devinsky et al. 1988). True vasculitis is very uncommon and the role of direct antibody-mediated damage is unresolved.

### Table 1: Diagnostic criteria for systemic lupus erythematosus

For the diagnosis of SLE, four or more of the following criteria should be present, either serially or simultaneously over any period of observation. (Tan et al. 1982).

- Malar rash
- Discoid rash
- Photosensitivity
- Mouth ulcers (oral or nasopharyngeal)
- Arthritis (nonerosive, involving two or more joints)
- Serositis (pleuritis + pleuritic pain or rub, OR pleural effusion, OR pericarditis, OR pericardial effusion)
- Renal disorder (persistent proteinuria > 0.5 g per day OR cellular casts)
- Neurological disorder (seizures OR psychosis)
- Hematological disorder (haemolytic anaemia OR leukopenia < 4000 on two or more checks OR lymphopenia < 1500 on two or more occasions OR thrombocytopenia < 100 000)
- Positive antinuclear antibody (in absence of drugs known to be associated with "drug-induced SLE")
- Anti-dsDNA OR positive antiphospholipid antibody OR false positive serological test for syphilis (positive for at least 6 months and confirmed by fluorescent treponema pallidum antibody absorption test).

### Table 2: CNS syndromes associated with systemic lupus erythematosus, in order of frequency (Jennekens et al. 2002)

- Depression
- Anxiety
- Psychosis
- Cognitive disorder
- Dementia
- Delirium/encephalopathy
- Epileptic seizures
- Stroke
- Transient ischaemic attack
- Tumour cerebri syndrome (benign intracranial hypertension)
- Chorea
- Parkinsonian syndrome
- Cerebellar syndrome
- Optic neuropathy
- Myelopathy
- Aseptic meningitis
It used to be thought that headache was a useful clinical pointer to CNS involvement in lupus but this turns out not to be the case (Sifakis et al. 1998). Indeed headache in SLE patients is most closely related to constitutional and systemic manifestations of the disease (Amit et al. 1999). In an important study, CNS involvement in SLE was significantly associated with cutaneous vasculitic lesions, livedo reticularis, thrombocytopenia, and a reduced serum C4 (Karassa et al. 2000). Interestingly, joint pain and the ‘discoid’ form of lupus rash were negatively associated with CNS involvement. But the greatest correlation with neuropsychiatric SLE was the presence of arterial thromboses elsewhere and the antiphospholipid syndrome (Tincani et al. 1996; Karassa et al. 2000). A survey of international opinion on neuropsychiatric SLE also highlighted the predominance of the antiphospholipid syndrome (Tincani et al. 1996).

Antiphospholipid syndrome

In 1952, a venous clotting disorder was described in two patients with SLE. Five years later a link was noted between recurrent pregnancy loss and the lupus anticoagulant. Then, in 1983, Graham Hughes – with whose name this disorder is strongly connected – described the association between antiphospholipid antibodies and arterial, as well as venous, thrombosis. These antibodies have been further characterized as being anticardiolipin antibodies, directed against the antigen β2-glycoprotein I. They are responsible for that earliest laboratory test for lupus: the false-positive test for syphilis. Anticardiolipin antibodies are common in the general population (6–45%). They are notoriously fickle; hence the usual requirement for repeated positive results over at least 6 weeks. A consensus is emerging on diagnostic criteria for the antiphospholipid syndrome (Table 3).

In retrospect, it is likely that most of the patients described in the original paper on ‘lupoid sclerosis’ (see below) in fact had the antiphospholipid syndrome.

Lupoid sclerosis

The term ‘lupoid sclerosis’ was coined in a paper published in Brain in 1972, from the Middlesex Hospital, with Michael Kremer as the senior author (Fulford et al. 1972). The term has haunted the literature ever since, and, as always with rather vague entities, undermined the confidence of diagnosticians. As discussed in the Summary box, they were probably cases of the antiphospholipid syndrome. This association has been explicitly suggested in recent years (Marullo et al. 1993; Dabadghao et al. 1995). Unlike the situation for most autoantibodies, there is no evidence for an increased prevalence of anticardiolipin antibodies in unselected multiple sclerosis populations (Cordoliani et al. 1998; Roussel et al. 2000; Heinzlef et al. 2002). However, a study from Jerusalem is telling. Karussis and colleagues looked for serum anticardiolipin antibodies in 70 patients with ‘classic’ multiple sclerosis and 100 with ‘unusual-for-M S’ patients who carried the diagnosis of multiple sclerosis but in whom there were atypical features (Karussis et al. 1998). All had MR scans that were regarded as typical for multiple sclerosis. 20 of these patients had consistently positive anticardiolipin antibodies and these were all in the atypical MS group: 15/20 had a myelopathy; 15/20 had optic neuropathy; and in 2/20 oligoclonal bands were positive. This result resonates with the consistent finding that approximately 1% of cases of SLE have a myelopathy or optic neuropathy, sometimes occurring together as Devic’s syndrome (summarized in Jennekens et al. 2002 and Scolding 1999).

A critical question, when considering the treatment of such Devic’s syndromes, is whether they are due to infarction or demyelination of

<table>
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<th>Table 3</th>
<th>Suggested diagnostic criteria for the antiphospholipid syndrome, preliminary criteria from Wilson et al. (1999)</th>
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<tbody>
<tr>
<td><strong>AT LEAST ONE CLINICAL CRITERION:</strong></td>
<td>Vascular thrombosis: one or more clinical episodes of arterial, venous or small-vessel thrombosis, in any tissue.</td>
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<tr>
<td>Complications of pregnancy:</td>
<td>One or more unexplained deaths of a normal fetus at or after 10 weeks gestation</td>
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<td>Three or more unexplained spontaneous miscarriages before 10 weeks gestation</td>
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<td>One or more premature births of a normal neonate before 34 weeks gestation</td>
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<td><strong>AT LEAST ONE LABORATORY CRITERION:</strong></td>
<td>Raised IgG or IgM anticardiolipin antibodies at moderate or high levels on at least two occasions, at least six weeks apart. (The definition of ‘raised’ is yet to reach a consensus; many laboratories use 15 or 20 international ‘id’ units.)</td>
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<td></td>
<td>Lupus anticoagulant antibodies detected on at least two occasions, at least 6 weeks apart</td>
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the optic nerve and spinal cord. There are very few pathological studies, but those that exist do not read like accounts of the pathology of regular multiple sclerosis. The spinal cord lesions affect white more than grey matter; there is necrosis and myelin vacuolization (Provenzale & Bouldin 1992; Matsumoto et al. 1997; Shin-taku & Matsumoto 1998). Whilst the potential association of the antiphospholipid syndrome with Devic’s syndrome is by no means proven, it is attractive on theoretical grounds. For Devic’s disease (that is Devic’s syndrome without identifiable cause) is believed to be one form of demyelinating disease that is caused by pathogenic antibodies rather than cell-mediated immune mechanisms (Lucchinetti et al. 2002), and there is some evidence that it is responsive to plasma exchange (Weinshenker et al. 1999).

Sjogren’s syndrome and primary progressive multiple sclerosis
It has been suggested that there is an increased prevalence of Sjogren’s syndrome amongst patients with primary progressive multiple sclerosis (de Seze et al. 2001; Thong & Venkatesubramanian 2002). There are even less data to support this claim than that for ‘lupoid sclerosis’. and Sjogren’s syndrome is almost as unrewarding to treat as primary progressive multiple sclerosis.

WHAT TESTS SHOULD YOU DO?

Blood tests
It follows from the above that a positive ANA in the context of a patient with presumed multiple sclerosis should lead to an ESR, full blood count

THE ORIGINAL ‘LUPOID SCLEROSIS’ PAPER
(FULFORD ET AL. 1972)
Michael Kremer and colleagues presented six case histories, all of which carried the diagnosis of multiple sclerosis and for which they offered the alternative diagnosis of SLE. Five of the cases had a progressive spastic paraparesis, without preceding relapses in three patients. None had had optic nerve involvement. In keeping with the standards of the day, none had brain imaging nor evoked potentials, nor were oligoclonal bands examined at that time.

Only one patient had systemic clinical features that would satisfy modern criteria for the diagnosis of SLE (arthralgia, fever and pleural effusion). In another case, there was no evidence for SLE at all, either clinical or laboratory: the diagnosis seems to have been made on the basis of chronic iridocyclitis and a raised ESR of 37 mm/h on one occasion.

All were described as having positive antinuclear antibody tests, but at most at a titre of 1 : 40; in two cases it was positive at 1 : 20, and in two other cases the ANA was only positive with neat serum which, by any standards, is a negative result. Using the same assay, they found that 10% of a cohort of 69 people with multiple sclerosis were positive for ANA.

However, four of the six patients had ‘scanty LE cells’ present in their peripheral blood – this largely historical test was said to be specific for SLE. And, perhaps most significantly, five patients had false positive tests for syphilis on at least one occasion, which we now know represents a lupus anticoagulant. No treatment was given to these patients.
(looking for lymphopenia and thrombocytopenia), renal function and anticardiolipin antibodies. A lupus anticoagulant test should also be performed; this may be positive in the absence of anticardiolipin antibodies. Abnormal antibody tests should only be regarded as significant if they are moderately or highly raised (and only discussion with your local laboratory will be able to define this), and if they are consistently raised in samples taken at least 6 weeks apart.

Spinal fluid analysis
CSF is less likely to be abnormal in patients with CNS involvement by lupus or the antiphospholipid syndrome compared to regular multiple sclerosis (Karussis et al. 1998; Scolding N 1999). However this is not absolute enough to be clinically useful.

MR imaging
Cerebral imaging may be normal in patients with neuropsychiatric lupus presenting as headache, psychosis, depression or seizures where the pathology may either be mediated by antibodies or lie outside the nervous system. This lack of tissue specificity about the diagnosis of neuropsychiatric lupus may explain why radiological abnormalities were found equally amongst SLE patients thought clinically either to have, or not to have, CNS involvement (Sabbadini et al. 1999). Non-specific white matter abnormalities are found in about one-third of cases of SLE without apparent neurological involvement (Kozora et al. 1998).

It is often the case that MR imaging of patients with CNS involvement by SLE or the antiphospholipid syndrome is reported as ‘consistent with demyelination’ or some such phrase. Whilst it is true that experts cannot always distinguish between these syndromes (Miller et al. 1987), it is equally true that MRI reports can be misleading (Figs 1 and 2). It is possible for frankly ischaemic lesions to be misdiagnosed in this way; perhaps wider use of diffusion-weighted imaging will prevent this. In patients with clinical evidence of cerebral neurological involvement, asymptomatic spinal cord lesions are far less common in lupus than multiple sclerosis. In an Italian study nine out of 10 multiple sclerosis patients had spinal lesions, which were not found in any of 24 patients with SLE, five Behcet’s, nine Wegener’s and six with the antiphospholipid syndrome (Rovaris et al. 2000). However, where there is a clinical myelopathy in SLE, it tends to be much more substantial than is usual in multiple sclerosis, extending through several segments, and so termed ‘longitudinal myelitis’ (Tellez-Zenteno et al. 2001).

Tissue diagnosis
The treatment of cerebral lupus may be prolonged and risky. Under the circumstances, many physicians would prefer a tissue diagnosis before embarking on treatments such as cyclophosphamide. If skin lesions are present, which is unusual, that is straightforward. Any hint of renal involvement makes the situation easier, for a renal biopsy is critical to diagnosis and prognosis of renal outcome (Esdaile et al. 1991). However most renal physicians are against renal biopsy in the face of normal renal function. Cerebral biopsy is rarely helpful (Fig. 2) and only advisable when there are radiological abnormalities to chase.

TREATMENT OF CEREBRAL LUPUS
There is little evidence base to the treatment of cerebral lupus. A logical approach nonetheless is to build a treatment strategy around the various possible pathogeneses:
- ischaemia due to thromboses secondary to the antiphospholipid syndrome;
- small-vessel non-inflammatory proliferative vasculopathy due to cell-mediated immune mechanisms;
- antibody-mediated damage to spinal cord and optic nerve (akin to Devic’s disease).

The generally accepted secondary preventive therapy of thromboses in the context of the antiphospholipid syndrome is anticoagulation, although there is no randomised clinical trial to prove this. It is clear that aiming for an INR of 2.0–3.0 is as good as at reducing the risk of further events than more intensive anticoagulation (Crowther et al. 2003). If thromboses continue in the face of adequate anticoagulation, immunosuppression is often used, although there is no good evidence for this approach. The standard treatment for the non-thrombotic syndromes associated with SLE is immunosuppression, first with corticosteroids and with early recourse to cyclophosphamide. A Cochrane review found no randomised controlled trials comparing these two treatments and concluded there was no evidence of a treatment advantage of cyclophosphamide (rather than ‘evidence of no effect’) (Trevisani et al. 2000). The immediate goal of management is to induce remission; anecdotally, pulsed IV cyclophosphamide achieves this more rapidly than oral. The adverse effects of cyclophosphamide accumulate with expo-
Figure 1 A man who carried the diagnosis of possible multiple sclerosis for a decade. His normal CSF at presentation led to a search for other causes, which proved negative. However, a second round of investigations into alternative causes, years later, revealed consistently high anticardiolipin antibodies and the lupus anticoagulant. On review, his MR brain scan originally reported as ‘consistent with multiple sclerosis’ was felt much more likely to be ischaemic, as were his ‘relapses’. He was anticoagulated.

Figure 2 A young woman who presented with dysphasia and cognitive impairment. An ANA was ‘moderately positive’ and her MRI was considered atypical for multiple sclerosis. So she had an angiogram, which was normal, and a brain biopsy, which showed typical inflammatory demyelinating lesions. She was put on immunotherapy. In retrospect this was a spurious ANA result.
Routinely checking the ANA, and arguably anticardiolipin antibodies as well, in patients suspected of having multiple sclerosis is cheap, easy and has the chance of revealing unsuspected treatable conditions. Can the same be said of lumbar punctures?

sure to the drug, so switching early to less toxic immunosuppressants is desirable, but there has been concern that this leads to a relapse. Now a randomised trial of the treatment of the ANCA positive vasculitides has shown that switching cyclophosphamide to azathioprine, combined with corticosteroids, at remission is as efficacious as continued cyclophosphamide treatment (Jayne et al. 2003).

The treatment of Devic’s syndrome, isolated myelopathy or optic neuropathy associated with the antiphospholipid syndrome or lupus has not been studied at all. Their lack of pathological similarity to classical multiple sclerosis means treatments such as interferon-beta cannot be justified. It is also hard to imagine that progressive ischaemia of isolated anatomical sites is responsible, so anticoagulation does not seem indicated. However, it might be reasonable to propose that the syndrome is caused by circulating pathogenic antibodies. Treatment with steroids and cyclophosphamide are routine in treating other life-threatening antibody-mediated diseases (such as antiglomerular basement membrane disease). So also is the use of plasma exchange, which because of the analogy with non-lupus Devic’s disease (Weinshenker et al. 1999), is particularly attractive as a treatment for these syndromes.

At the outset of treatment, it is important to identify an objective marker of disease activity to guide treatment withdrawal or escalation prior to tissue damage. Ideally this would be a simple blood test (ESR, antibody titre). But this is not always found and, furthermore, it is not necessarily the case that neurological disease will follow systemic disease activity. Relying on patients’ symptoms is notoriously unreliable when so often there are the confounding effects of systemic illness and depression. If resources allowed, in a dedicated clinic, systematic administration of quality of life scales (such as the SFD 36) and psychometry would be helpful. But often the only marker of neurological lupus is the rate of lesion acquisition between serial MR images. However, just as with multiple sclerosis, there is no consensus on the significance of radiological lesion formation and how it should influence treatment.

Neurologists have traditionally treated cerebral lupus (and other immunological conditions affecting the nervous system) rather conservatively, leading to the ridiculous situation that damage to the kidney or lung in systemic diseases is treated more aggressively than damage to the brain.

In centres dedicated to the treatment of lupus, a variety of drugs are used in addition to steroids and cyclophosphamide, including anti-B cell monoclonal antibodies, tacrolimus, mycophenolate and even intrathecal cytotoxics (Dong et al. 2001). Not all neurologists are comfortable with these agents, whereas their use is routine to many physicians, who themselves are usually uncertain about the neurological syndromes. Therefore cerebral lupus, like the neurological vasculitides, is best managed jointly by neurologists and clinical immunologists, renal physicians, rheumatologists or the like.
SUMMARY – WHAT TO DO WITH THE MULTIPLE SCLEROSIS PATIENT WITH A POSITIVE ANA

Define the neurology  Syndromes consistent with arterial or venous thromboses should raise the possibility of infarction due to the antiphospholipid syndrome. Devic’s syndrome, an isolated myelopathy or optic neuropathy may reflect antibody-mediated white matter damage akin to Devic’s disease.

Check for systemic features of SLE and the antiphospholipid syndrome  Almost certainly the patient’s obstetric record will not be recorded and yet this is critical to the diagnosis of the antiphospholipid syndrome (miscarriages). Livedo reticularis and a vasculitic skin rash are particularly associated with CNS lupus and the antiphospholipid syndrome; arthralgia and discoid lupus less so. Do not forget the urine dipstick!

Scrub the ANA result  A positive result is much more likely to be of clinical significance if in high titre and replicated over time.

Review the MR imaging  Do not be content with a report ‘consistent with multiple scleroris’. If the presenting syndrome is cerebral, then a spinal MRI is much more likely to be abnormal in multiple sclerosis than in SLE. If the patient has a myelopathy, the lesion will be more extensive in SLE than multiple sclerosis.

Blood tests  Check the blood count, renal function, ESR and both anticardiolipin antibodies and the lupus anticoagulant, which is often forgotten. One positive result on any of these does not make a diagnosis.

Chase a tissue diagnosis  Especially skin or renal.

Treatment  Patients who have had thromboses due to the antiphospholipid syndrome should be anticoagulated (evidence that INR 2.0–3.0 is as good as more intensive anticoagulation); if thromboses continue consider immunosuppression (little evidence). For non-thrombotic lupus syndromes use corticosteroids, with cyclophosphamide if severe (standard practice, little evidence), switching to steroids and azathioprine at remission (evidence from the treatment of vasculitis). For Devic’s syndrome, myelopathy or optic neuropathy, consider the early addition of plasma exchange (evidence from nonlupus Devic’s disease).

Do not be afraid to refer!  These diseases, mysterious to many neurologists, are the bread and butter of someone near to you.

SHOULD AN ANA TEST ALWAYS BE PART OF THE DIAGNOSTIC WORK-UP FOR MULTIPLE SCLEROSIS?

Routine checking the ANA, and arguably anticardiolipin antibodies as well, in patients suspected of having multiple sclerosis, may seem burdensome when a positive result is most likely to be spurious, and the association of any demyelinating syndrome with lupus is unproven. But it is cheap, easy and has the chance of revealing unsuspected treatable conditions. Can the same be said of lumbar punctures?

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Looks Like Multiple Sclerosis, but the Ana is Positive: Does My Patient Have Lupus?

Alasdair Coles

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