actual presence of the parvovirus has not yet been shown in fifth disease, probably because the viraemia occurs during the incubation period and has waned before the rash is conspicuous. If this is so, it will be impossible to make a definite association between the B19 parvovirus and the disease until patients are studied in the phase before the rash appears. Nevertheless, every outbreak examined has had serological evidence of recent parvovirus infection, and it begins to seem that the virus is the exclusive cause of the disease.

Much remains to be done. Studies are needed on the excretion and spread of the parvovirus. Although dot hybridisation with labelled viral DNA sequences now offers an alternative method of detection (Clewley JP, Anderson MJ, personal communications), the virus still cannot be isolated from body fluids and propagated in tissue culture. The incubation period of parvovirus related fifth disease has to be established, as have its haematological features, its complications, and the proportion of infections that are subclinical. It is particularly important to look for any effect on the fetus or newborn. Lastly, the definition of the disease ought to be reconsidered. Fifth disease was a name coined to assert that the disease was distinct from other erythematous illnesses of childhood.[2] It has no descriptive value and has probably survived only because it falls from the tongue more easily than "erythema infectiosum." If the name is retained, it should be clear what is meant by it. In its sporadic form fifth disease cannot always be recognised clinically, but a serological test for the human parvovirus will clarify the diagnosis when the condition is suspected. In fact, after 80 years of imprecision, fifth disease might now be defined as "that acute erythematous illness which is due to the human parvovirus."

P P MORTIMER

Consultant Microbiologist,
PHLS Virus Reference Laboratory,
London NW9 5HT

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Regular Review

Autoantibodies in lupus and its variants: experience in 1000 patients

GRAHAM R V HUGHES

In 1970 a lupus clinic was started in the rheumatology unit at the Hammersmith Hospital, and between 1973 and 1983 clinical and serological studies were made on over 1000 patients with lupus and lupus-like diseases. The apparent increase in the prevalence of systemic lupus erythematosus in Britain mirrors that seen in countries throughout the world —an increase presumably due at least in part to the development of more sensitive diagnostic tests and a recognition of many milder forms of the disease.

In parallel with this increased awareness of systemic lupus erythematosus has come the more precise clinical and serological definition of several clinical features previously thought to be heterogeneous or unrelated. Recently, for example, a syndrome has been described consisting of multiple thromboses, multiple abortions, disease of the central nervous system, livedo reticularis, and labile hypertension.[1,2] Patients with this syndrome have many of the features of lupus but their sera are often negative for antinuclear antibody and show high titres of anticardiolipin antibodies.

For every patient with a butterfly rash, pleurisy, and nephritis there are probably many more with atypical disease. Furthermore, conditions such as idiopathic thrombocytopenic purpura, Sjögren's syndrome, Raynaud's phenomenon, and congenital heart block are clearly related to systemic lupus erythematosus. One approach to such "overlap" syndromes has been the study of different autoantibodies and their possible matching with clinical subsets. Though this concept may smack of "stamp collecting," it is already producing results with clinical relevance to the practising physician.

Antinuclear antibodies

Standard testing for antinuclear antibodies (using, for example, rat substrates) still provides the screening test for systemic lupus erythematosus. Tests based on more rapidly dividing cell preparations (such as HEp_2 cells or fibroblast cultures) may possibly be more sensitive but the results they

give are, by definition, different. In any event, refinements of methods for testing for antinuclear antibodies have been made obsolete by techniques such as Farr immunoassay, counterimmunoelectrophoresis, and immunoprecipitation.

The number of nuclear antigens now characterised is increasing rapidly. They are broadly classified into those characterised chemically, such as double stranded DNA, histones, and so on, and a second group of nuclear and cytoplasmic antigens which are largely saline extractable (ENAs—table I). Antihistone antibodies are found in systemic lupus erythematosus, and in certain drug induced syndromes such as procainamide lupus.[3] Possibly in the future, detection of antibodies against different histones may provide a means of "fingerprinting" drug induced lupus syndromes. For over a decade now, however, measurement of anti-DNA antibody has remained the diagnostic yardstick for systemic lupus erythematosus.[4]

TABLE I—*Antinuclear and anticytoplasmic antibodies*

Antigen		*Disease association*
Group 1: DNA and histones		
Antidouble-stranded DNA	→	Systemic lupus erythematosus
Antisingle-stranded DNA	→	Non-specific
Antihistone	→	Procainamide lupus erythematosus (90%)
Group 2: Non-histone antigens		
Predominantly saline soluble nuclear and cytoplasmic ribonucleoproteins (ENAs)	→	SLE, myositis, Raynaud's, and "overlap" syndromes

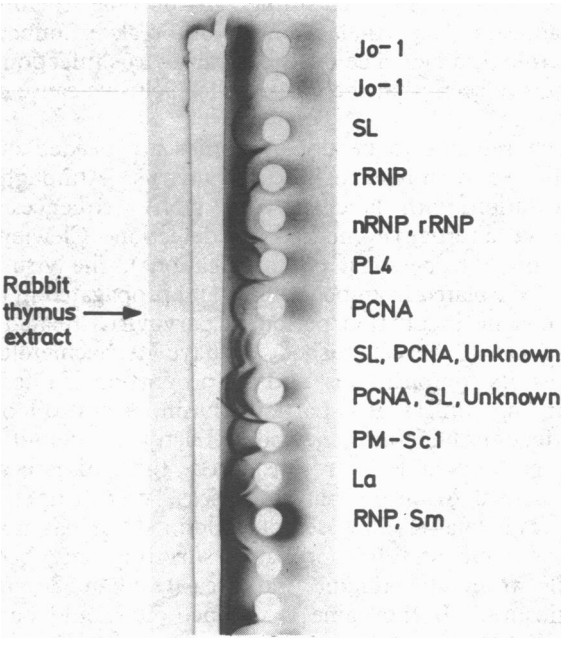
This clinical review is concerned with the second group—the saline extractable nuclear antigens. Our data are based on serological testing on 1018 patients with lupus and other connective tissue diseases seen in the rheumatology unit, Hammersmith Hospital, between 1973 and 1983, the details of which are to be published elsewhere.[5]

Extractable nuclear antigens

In the past decade, largely through the work of Reichlin, Tan, and others, the clinical and biological importance of extractable nuclear antigens has become widely appreciated. Their detection is now cheap, reproducible, and simple. The method devised by Bunn[6,7] based on the method of Kurata and Tan[8] takes one hour, uses a drop of serum, and brings measurement of extractable nuclear antigens within the scope of all service laboratories. With this method the presence of several extractable nuclear antigens in a test serum can be identified by comparing precipitin lines with those of known serum controls now widely available (figure).

Over 20 such systems are now recognised and the more important, with their main clinical associations, are listed in table II. More comprehensive reviews are provided elsewhere.[9-12]

Insights into the molecular structure of a number of extractable nuclear antigens have come from techniques such as immunoprecipitation using cells cultured with radiolabelled phosphorus or amino acids to obtain labelled RNA or proteins which can then be precipitated by antibody or "Western" blotting using nitrocellulose membranes. Some antigens are naked protein but most are soluble ribonucleoproteins, either predominantly nuclear (Sm and RNP) or cytoplasmic (Ro, Jo-1). Some of the antigens exist together in macromolecular complexes. Thus Sm antisera can precipitate both Sm and RNP. Jo-1 has been shown to be directed against histidyl-tRNA synthetase.[13] Possible antibodies to extractable nuclear antigens may not only prove to be useful probes for cell biologists but may directly influence messenger processes within the cell.



Testing for extractable nuclear antigens by comparing precipitin lines with those of known serum controls (see tables II and III for explanation of symbols).

TABLE II—*Principal extractable nuclear antigens*

Antigen	*Disease association*
Sm	SLE (7% in white individuals; 30% in blacks and Chinese)
Ro ("SSA")	SLE
	Antinuclear antibody negative lupus
	Sjögren's syndrome
	Congenital heart block
	? ITP
La ("SSB")	SLE
	Sjögren's syndrome
RNP	MCTD (100%)
	SLE
Scl-70	PSS
Jo-1	Myositis
SL	SLE
XR/XH	CAH-PBC

SLE=systemic lupus erythematosus; ITP=idiopathic thrombocytopenic purpura; MCTD=mixed connective tissue disease; PSS=progressive systemic sclerosis; CAH=chronic active hepatitis; PBC=primary biliary cirrhosis; RA=rheumatoid arthritis.

Clinical importance

The extractable nuclear antigens have been of value in the clinical assessment of "overlap" syndromes, in which myositis, Raynaud's phenomenon, rashes, and Sjögren's syndrome figure prominently. Table III lists the frequency of some of the more important associations seen in our patients, including some collaborative data obtained with other centres. Although grey areas abound, some associations between antibody and disease are notably specific—those between anti-RNP and mixed connective tissue disease, anti-Ro and primary Sjögren's syndrome (as well as chronic cutaneous lupus erythematosus, see below), anti-Jo-1 and myositis-pulmonary fibrosis, and anti-XR in chronic active hepatitis. Some of these associations will be discussed in more detail.

Anti-RNP antibodies are found in high titres in a group of patients with Raynaud's phenomenon and synovitis of their

finger joints and tendons.[14] Though these patients appear to represent a fairly recognisable subset, the clinical and serological features of the syndrome may change with time, many patients ultimately progressing towards scleroderma and becoming "seronegative."[15] Anti-RNP antibodies are also seen in systemic lupus erythematosus (23%) and in myositis (14%). Apart from these groups the diagnostic specificity seems high, anti-RNP antibodies being found, for example, in only between 2% and 5% of patients with primary systemic sclerosis and 4% of patients with primary Sjögren's syndrome.

TABLE III—*Disease associations in 1018 sera from different connective tissue diseases seen at Hammersmith. The most important associations are italicised*

Antibody system	*Disease*								
	SLE	*MCTD*	*Primary Sjögren's syndrome*	*Myositis*	*PSS*	*RA*	*PBC*	*CAH*	*Other*
Sm	7	7	—	—	—	—	—	—	—
RNP	23	*100*	4	14	2·5	—	—	—	—
Ro	24	17	75	8	4	3	6	4	—
La	8	3	42	—	—	—	—	—	—
Jo-1	—	3	—	*25*	—	—	—	—	—
SL	6	3	—	—	—	—	—	—	—
Pm-Scl	—	—	—	11	—	—	—	—	—
XR	—	—	—	—	—	—	*10*	*11*	—
SCL-70	—	—	nd	—	16	—	nd	nd	—
Centromere	2	—	—	—	*29*	—	8	—	—
Mitochondria	—	—	4	—	—	—	*88*	2	—

SLE = systemic lupus erythematosus; ITP = idiopathic thrombocytopenic purpura; MCTD = mixed connective tissue disease; PSS = progressive systemic sclerosis; CAH = chronic active hepatitis; PBC = primary biliary cirrhosis; RA = rheumatoid arthritis.

Several antibodies directed against proteins associated with transfer RNA have been detected in myositis. One of these—anti-Jo-1—appears highly specific. It is rarely found in systemic lupus erythematosus but has been detected in a quarter of patients with polymyositis.[16] This subgroup of patients with polymyositis appears to have a high incidence of pulmonary fibrosis and a relapsing course. To date (though only time will tell) we have not detected anti-Jo-1 in cases of polymyositis associated with malignancy. The finding that anti-Jo-1 antibody is directed against the enzyme responsible for catalysing the charging of histidine to its transfer RNA leads one to reflect that some picornaviruses interact with transfer RNA synthetase enzymes. These include Coxsackie viruses, previously implicated by our group in the pathogenesis of some cases of polymyositis.[17]

Recognition that antibodies directed against nuclear and cytoplasmic extracts were found in patients with Sjögren's syndrome dates back to the work of Anderson *et al.*[18] Subsequently different groups of workers recognised that antibodies against two particular antigens—first called Ro and La—were particularly prominent in primary Sjögren's syndrome. Later, Tan and his colleagues independently reported these antibodies and gave them the titles SS-A and SS-B. SS-A and SS-B are now known to be identical with Ro and La respectively.

Sjögren's syndrome occupies a central position among the connective diseases. It is found in a significant proportion of patients with other connective tissue diseases and is a common isolated finding in older patients whose sera are found on routine testing to be positive for antinuclear antibody. Anti-Ro antibodies are found by most groups to be the commonest antinuclear antibody in patients with primary Sjögren's syndrome, being found in three quarters of our patients.

Dermatologists have long recognised that tests for antinuclear antibodies may prove negative in several patients with otherwise typical systemic lupus erythematosus (pleurisy, pericarditis, arthritis, rashes, and alopecia). Almost by definition it is impossible to know the incidence of such cases. Some of these patients with "antinuclear antibody negative" lupus have recurring photosensitive rashes (sometimes with a characteristic annular appearance—"chronic cutaneous lupus erythematosus"), Sjögren's syndrome, an excellent response to antimalarial treatment, and a low incidence of renal disease. Characteristically, only anti-Ro antibody is detectable—hence the frequently negative conventional test for antinuclear antibody.[19]

In addition to this syndrome, anti-Ro is found in other connective tissue diseases, notably in up to three quarters of patients with primary Sjögren's syndrome, and possibly—though yet to be confirmed—in a subset of patients with idiopathic thrombocytopenic purpura.[20]

Not only in these "overlap" groups of patients have tests for anti-Ro antibodies provided a useful additional diagnostic marker. They have already helped to highlight a link between systemic lupus erythematosus and an apparently unrelated condition, congenital heart block. Pregnancy is not usually contraindicated in systemic lupus erythematosus and children of patients with systemic lupus erythematosus are generally healthy; but a rare cardiac abnormality—congenital heart block—is seen in some of their offspring. This condition, with its generally benign prognosis, may be handed down through more than one generation.[21] Studies of mothers of children with congenital heart block have shown that up to one third had systemic lupus erythematosus or a systemic lupus erythematosus variant and that up to two thirds had circulating anti-Ro antibodies.[22]

"Speckled" and antinuclear patterns of antinuclear antibody have been recognised as common features of patients with scleroderma for many years. The predominant antinuclear antibody in scleroderma is anticentromere, being found in 29% of our patients. This antibody (demonstrable particularly well on HEp_2 cell preparations with rapidly dividing cells and prominent chromosomes and centromeres but not detected by routine counterimmunoelectrophoresis) is found in up to 80% of patients with CREST syndrome (calcinosis, Raynaud's, (o)esophagitis, sclerodactyly, and telangiectasia) and 8% of patients with primary biliary cirrhosis.[23]

Another antibody in scleroderma is directed against scl-70, a basic protein of 70 000 daltons, and is found in some 16% of patients; it seems to be reasonably specific for this disease.

Antimitochondrial antibodies are the most well recognised marker in primary biliary cirrhosis, occurring in almost 90% of patients studied in collaboration with the group in King's College Hospital. Other antinuclear antibodies are seen, however, and, in future, may come to have some diagnostic importance. One such antibody, designated XR, was found in almost a quarter of patients with chronic active hepatitis.[24]

Much as the titre of anti-DNA antibody may change, so also may the titres of other antinuclear antibodies such as anti-RNP and anti-Ro. Furthermore, in our own retrospective studies occasional patients have over the years changed not only the character of their disease but their antinuclear antibody profile.[5] Only prospective studies will tell how closely these changes parallel each other and how useful changes in antinuclear antibodies will prove in assessing prognosis and management.

Antiphospholipid antibodies

So far this review has concentrated on relatively minor, though useful, links between antinuclear antibody specificity and disease. Recently, however, we have studied a group of

antibodies which promises to have considerable diagnostic and pathogenetic implications. These are the group of antibodies directed against phospholipid antigens, which is widespread in nature—for example, in endothelial cell membranes, platelets, brain tissue, and so on.

Two of these antibodies—anticardiolipin (used in crude form in the Wassermann reaction) and an antiphospholipid ("lupus anticoagulant") have been recognised as being associated with thrombosis and abortion in patients with systemic lupus erythematosus. Recurrent venous thrombosis and recurrent spontaneous abortion are features of some patients with systemic lupus erythematosus. These features, together with livedo reticularis and labile hypertension, have recently been emphasised as a syndrome in some patients who may or may not have antinuclear antibodies.[1 2] In studying the lupus anticoagulant in our patients we found that 18 out of 31 patients with a positive test for the antibody had a history of venous or arterial thrombosis. Of the 26 women with lupus anticoagulant activity, nine had had one or more abortions.[25] Of seven patients with systemic lupus erythematosus and pulmonary hypertension, five had lupus anticoagulant activity, which suggests that intrapulmonary arterial coagulopathy may be an aetiological factor.[26]

The traditional tests for these antibodies—the Wasserman reaction or Venereal Disease Research Laboratory and the lupus anticoagulant test—had severe limitations and we have developed more sensitive immunoassays. The first of these, a solid phase radioimmunoassay for anticardiolipin, is up to 400 times more sensitive than the Venereal Disease Research Laboratory test.[27] In clinical studies striking associations were noted with thrombosis, especially cerebral thrombosis,[28] abortion, and thrombocytopenia.[29] Subsequent studies have already shown that the antibody is associated with some other types of disease in which thrombosis has been prominent, including Degos's disease[30] and Behçet's syndrome.[31]

In view of the possibility that certain antiphospholipid antibodies may cross react with epitopes on cerebral phospholipids such as sphingomyelin,[32] it was interesting to observe high titres in two patients with acute neurological disease—acute Guillain Barré syndrome[33] and lupoid sclerosis (Harris EN, unpublished observations). These antiphospholipid antibodies may have considerable pathogenetic as well as diagnostic importance in certain thrombotic and neurological syndromes.

Conclusions

Newer, more sensitive techniques have increased our knowledge of the molecular biological characteristics of some antinuclear antibodies and their clinical associations. In less than two decades testing for antinuclear antibodies has moved from the visual impression of fluorescent patterns to molecular characterisation of many of the antigens. This has already helped the clinician in the diagnosis of clinical subsets, though definition is far from precise. The clinical importance of extractable nuclear antigens, however, appears small when compared with the potential clinical and pathogenetic importance of antiphospholipid antibodies, such as the recently described anticardiolipin antibody.[27] The associations of this antibody with thrombosis, abortion, thrombocytopenia, and neurological disease promise implications far beyond connective tissue diseases.

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GRAHAM R V HUGHES
Consultant Physician and Reader in Rheumatology,
Royal Postgraduate Medical School,
London W12 0HS

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