Report of symposium

Antinuclear antibodies and their clinical significance*

This Symposium, jointly sponsored by the Heberden Society and the Arthritis and Rheumatism Council, was held at the Royal Postgraduate Medical School, London, on January 8, 1976. The speakers discussed the nature and source of nuclear antigens which induced an immune response, their role in immune response, methods of detection of antibodies, their role in pathogenetic mechanisms and their clinical relevance.

Nuclear antigens and antigen-antibody reactions

Dr. D. Stollar (Tufts University, Boston, Mass., USA) discussed the origin and types of polynucleotide antigens to which antibodies occur in systemic lupus erythematosus (SLE), stressing that DNA and RNA were not the only antigens to which antibodies are found in SLE. In general, studies of the specificity of antibodies had not confirmed or eliminated a viral infective aetiological hypothesis for the disease. Some antibodies in SLE sera are directed against purine or pyrimidine bases while others appear to be directed against the sugar-phosphate backbone; antibodies that react with double-stranded DNA (ds-DNA) may recognize the sugar-phosphate backbone of one strand of the helix (Stollar, 1973, 1975). Antibody reactions with DNA occurred irrespective of whether they were of plant, viral, bacterial, or mammalian source, and this approach could not distinguish between viral or host origin of DNA.

Antibodies to double-stranded RNA (ds-RNA) have a distinct specificity. The antigenic determinant may involve the backbones of both strands of the helix over a range of three or four base pairs as it does with experimentally induced antibodies (Stollar, 1973, 1975). While ds-RNA may be a more characteristic viral form of nucleic acid, some of this polynucleotide does occur in uninfected mammalian cells, and the presence of such antibodies cannot distinguish with certainty between the viral and host forms of RNA. SLE sera also react with synthetic RNA-DNA hybrids (Talal and Gallo, 1972); however, they show a less distinct specificity than do experimentally induced anthybrid antibodies (Talal and Gallo, 1972; Stollar, 1975). The hybrids could be produced by the action of the reverse transcriptase of oncornaviruses, but the serological reactions of the hybrids with SLE sera may represent cross-reactions of antibodies to ds-DNA or ds-RNA (Talal and Gallo, 1972); thus they could not be regarded as providing certain and specific evidence of viral infection.

It is difficult to experimentally induce antibodies to ds-DNA in the normal animal (however, they are found spontaneously in the nude and NZB mouse which have deficient thymic function) suggesting that the host factors are important in the development of reactivity to DNA in SLE. Other antigens reactive with SLE sera, such as free histone, nucleohistone, ribonucleoprotein, or soluble nuclear proteins, seem more likely to be of host origin. Stollar concluded that if viral infection is responsible for SLE, it cannot be merely acting by providing polynucleotide antigens, since the disease is characterized by hyper-reactivity to a variety of antigens, several of which are probably of host and not viral origin.

He summarized the evidence for a viral aetiology:
(a) Inclusion bodies similar to viral material are found in SLE—though this is not a consistent finding nor is it specific for SLE.
(b) Antibodies to viruses are raised; this parallels the general hyperglobulinaemia in the disease and does not appear to be a specific response to a virus responsible for the SLE.
(c) Antinuclear antibodies may represent a response to viral material.
(d) In animal models similar diseases have been transferred with cell-free extracts; however, in the SLE-like syndrome in dogs, Lewis, Andre-Swartz, and Harris (1973) have been unable to show viral particles in the filtrates and it has been suggested that the material may be activating virus already present in the recipient.
(e) Murine viral antigens have been shown on human SLE lymphocytes (Schwartz, 1975).
(f) Viral genome sequences have been detected in DNA from patients with SLE (Zhadanov, 1975).

Some of the factors influencing interactions between DNA and antibodies were discussed by Dr. L. A. Aarden (Plesmanlaan, Amsterdam, Netherlands) (more became apparent in the ensuing workshop). Using serum from a patient with SLE as a source of anti-DNA antibodies, radiolabelled DNA from different mammalian, viral, and phage sources gave a percentage binding which varied.

* Report prepared by P. J. L. Holt, Rheumatism Research Centre, Manchester University Medical School, and R. N. Maini, Kennedy Institute and Chartering Cross Hospital, London.
from 5–95% in the Farr test. He felt that these variations could be entirely ascribed to variations in the molecular weight of the DNA; the higher the molecular weight of DNA, the greater the binding. Up to a molecular weight of 10^7 serum DNA binding is linearly related to the molecular weight in the Farr test indicating that in this primary binding assay one molecule of antibody is sufficient to precipitate one molecule of DNA.

In addition to heterogeneity of molecular size, the purity of ds-DNA is important since there is evidence that single-stranded DNA (ss-DNA) antibodies show less specificity than ds-DNA for SLE. For most clinical purposes the detection of antibodies to ds-DNA is the most important step. Contamination with ss-DNA, usually in small but variable amounts, or breaks in the double-strand leading to exposure of single-stranded regions is common, and reaction with these antigenic sites may give rise to 'false-positive' results. The use of circular DNA from the phage PM2 avoided both variations in molecular weight and contamination with single stranded regions. Dr. R. M. Bennett (Pritzker School of Medicine, Chicago, Ill., USA) (Sukhupunyaraks and others, 1976) presented data on a method for purification of ds-DNA by removal of the molecules containing single stranded regions by a single-strand specific nuclease and chromatography on BND cellulose (benzoylated naphthylated di-ethylaminoethyl cellulose). In his experience the use of pure ds-DNA also improved the specificity of the technique for the diagnosis of SLE. This is, however, difficult to achieve and maintain largely because of deterioration of the DNA with storage.

Dr. Aarden next discussed the type of antibody response. He suggested that the immunoglobulin class of DNA antibody may vary with the stage of the disease, and similarly that the avidity of the antibody may be important in determining the type of disease and clinical picture produced (discussed in a later section of the report). He suggested that antibody avidity may also determine the degree of binding to ds- and ss-DNA, as low avidity antibody may be expected to show relatively greater avidity for ss-DNA because both antibody sites of IgG might attach to antigenic sites on the flexible structure of a single ss-DNA molecule, whereas binding might be restricted to a single site on the rigid ds-DNA molecule. He speculated that the sera which have been observed to give positive reactions for anti-ds-DNA antibodies using *Crithidia luciliae* as a substrate in an immunofluorescent technique, but do not bind ds-DNA in a Farr assay, may also be explained on the basis of avidity; low avidity antibody complexes dissociate in fully saturated ammonium sulphate whereas the same antibody binds to the DNA in the kinetoplast of the *Crithidia* and is not removed by the washing procedure.

Even the use of a pure antigen does not overcome the problem that free and bound DNA may be present in the serum under test. DNase treatment may help by freeing bound DNA antibody but it is not certain if this is the complete answer since there is doubt that significant amounts of DNA antibody can be recovered by this method (E. V. Barnett, University College, Los Angeles, Calif., USA).

**Pathogenesis of autoimmune complex diseases**

The pathogenesis of immune complex disease with particular reference to SLE was considered next. Dr. N. Talal (Veterans Administration Hospital, San Francisco, Calif., USA) reviewed the immunopathology of the prototype animal model of SLE, the New Zealand mouse, highlighting the features suggestive of immunological 'dysgeneration' characterized by loss of regulation of normal immunity most probably at the level of function of T helper and suppressor cells. He noted the following: a genetic predisposition to autoimmunity; progressive development of LE cells and antibodies to nucleic acids; progressive onset of immunopathology; and immunological imbalance between decreased cellular immunity (T-cells) and increased antibody responses (B-cells). Expanding on his concept of progressive immunological dysgeneration, he pointed out that many types of autoantibodies appeared progressively and the class of antibody to DNA and poly A changed from 19S (IgM) to 7S (IgG) in type (this switch occurring at different times for the two antigens suggesting that different mechanisms for each are involved). The switch to IgG production appeared at an earlier time and with more severe kidney disease in the female than in the male. It was suggested that this change reflected a basic T-cell abnormality. Other features of T-cell deficiency are found in both nude and thymectomized animals; these include a reduced number of T-cells whose function is defective, and later in life there is the appearance of malignancy and in particular of lymphocytic tumours and an inability to deal with viral infection.

Turning to human diseases, Dr. Talal reviewed his work with families of SLE patients (Dehoratius and others, 1975). Although the patients tended to have 7S antibodies to DNA and RNA, the cohorts tended to have 19S rather than 7S antibodies. This was most marked for RNA antibodies and in consanguineous relatives. Similar changes are found for lymphocytotoxic antibodies. After successful treatment the antibody type progressively reverts from 7S to 19S in type.

Dr. A. M. Denman (Clinical Research Centre, Harrow, England) considered two aspects of cell-
mediated immunity in the connective tissue diseases. The first concerned the possibility that the defect in lymphocyte function described in these disorders is no more than a secondary, perhaps nonspecific, reflection of disease activity. A prospective study of proctolol-induced autoimmunity (Raftery and Denman, 1973) has clearly indicated that the lymphocyte abnormalities follow and do not precede the development of autoantibodies. He felt it unlikely, therefore, that the current techniques have shown any pre-existing 'T lymphocyte deficiency' in these disorders. Secondly, there is evidence that lymphocytes in autoimmune diseases possess antiviral activity and therefore may be expected to participate in the host response to putative viral infections, but their role in production of disease is unresolved (Denman and others, 1975). The approach of Talal and Denman to the investigation of autoimmune diseases needs to be reconciled to the observed diversity of the clinical syndromes, and of SLE in particular.

The role of circulating immune complexes in mediating inflammation in rheumatic diseases is now well recognized; their composition and detection are subjects of current research. Dr. P. H. Lambert (Divisions d'Hematologie des Services de Medicine, Geneva, Switzerland) reviewed their findings with the radiolabelled C1q binding test for complexes in serum of patients with SLE (C1q, a subunit of the first component of complement, binds to soluble complexes and is thus a method of detecting immune complexes independently of the antigens involved). Although C1q can also bind to DNA (which may circulate as free antigen in SLE), the conditions under which the test is performed, using 3–4% polyethylene glycol for precipitation of C1q bound to complexes, does not lead to the precipitation of any free DNA present. Some evidence has been presented recently by other workers that DNA-anti-DNA antibody complexes circulate in the blood of patients with SLE, but since treatment of the serum with DNase had no appreciable effect in reducing the amount of immune complexes detected by the C1q test DNA-anti-DNA component of the circulating complexes was probably small. If the DNA-anti-DNA component of circulating complexes is so small, the question arises as to why DNA-anti-DNA constitute an important part of the complexes deposited on the glomerular basement membrane (GBM) of the kidney. An attractive explanation was put forward by Lambert who had separated GBM material and shown that this preparation had a 100-fold increased affinity for DNA than for plasma proteins (purified collagen also appears to bind DNA very efficiently). In an experimental model of glomerulonephritis induced by injection of lipopolysaccharide the sequence of events in the kidney appeared to initially involve binding of circulating DNA to GBM, followed by interaction with circulating anti-DNA antibodies over the subsequent few days.

Further support was forthcoming from experiments in which radiolabelled DNA injected into mice is initially attached to many tissues but tends to persist only in renal tissue. The implication of these experiments is that immune complexes of DNA-anti-DNA activity in SLE kidneys may be formed locally, rather than as a result of deposition of preformed complexes from circulating blood. In spite of the doubts that the C1q test may not detect DNA-anti-DNA complexes, in practice it correlates well with the activity of the disease, implying that the circulating complexes (whatever their composition) may be of additional significance. Further work was being carried out to determine the composition of the C1q reactant.

Dr. R. H. Zubler (WHO Immunology Research and Training Centre, Geneva, Switzerland) presented evidence that C1q binding material in the sera and synovial fluids from patients with rheumatoid arthritis occurred in the immunoglobulin-rich fractions. A discrepancy has been found in the precipitation tests with C1q which are positive in SLE but negative in rheumatoid arthritis and those radiolabelled C1q binding test which is positive in both. It was suggested that the C1q binding tests are probably more sensitive because polyethylene glycol encourages the precipitation of 'small' complexes found in rheumatoid arthritis, whereas only 'larger' complexes precipitate in agar.

The presence of complement is a prominent feature of the immune complex lesion. Professor P. J. Lachmann (MRC Laboratory of Molecular Biology, University of Cambridge, England) reviewed the part played by complement in tissue damage usually as a result of activation by local deposition of complexes, although biologically active components could be produced elsewhere and transported to the site of inflammation. The actual damage is due to the secondary presence of activated polymorphonuclear leucocytes which released enzymes. Activation of the early components of complement results in the attraction and immobilization of polymorphs at the site of damage as well as contributing to increased vascular permeability which results in complex localization. The latter lytic complement components are not essential for immune complex tissue damaging reactions since their deficiency does not alter the disease process. Complement independent immune injury also occurred, especially in the kidney.

The wide range of infective agents that might give rise to immune complex diseases was noted, as was the association between some of the rare complement deficiency syndromes (predominantly involving C1, C2, C4) and immune complex diseases.
including glomerulonephritis, Henoch-Schönlein disease, and SLE. Lachmann discussed three possible reasons for this association; firstly, the possibility of abnormally high ascertainment because of the rarity and thus fuller investigation of rare complement deficiencies, but decided that this was probably not a factor. Secondly, the failure of pathogen elimination because of complement deficiency, which was a strong possibility; and thirdly, the explanation could be that there was a linkage between the disease facilitating genes and the genes controlling complement synthesis, i.e. a genetic abnormality controlling inheritance of both defects.

The relationship of genes controlling complement synthesis to histocompatibility antigens was elaborated by Dr. D. N. Glass (Robert B. Brigham Hospital, Boston, Mass., USA) who had investigated families homozygote and heterozygote for C2 deficiency by employing both functional and immunochemical assays (the total absence of C2 indicating a homozygote and 50% levels a heterozygote state). In studying families of index cases the HLA haplotypes A.10 and B.18 were found in all the affected members of the families. Although C2 deficiency is a rare finding in the general population, it occurs in an increased incidence of SLE patients and in juvenile rheumatoid arthritis. There was some evidence that autoimmune diseases occurring in association with complement deficiencies had some atypical features; for example, in the lupus syndrome antinuclear antibody is less frequently found and occurs in lower titres, and the onset of juvenile rheumatoid arthritis tends to occur at a younger age.

Antinuclear antibody (ANA) measurement and clinical significance

Dr. E. J. Holborow (MRC Rheumatism Unit, Taplow, England) reviewed the techniques available for detecting ANA and emphasized that most tests represented a secondary stage of detection of the antibodies and thus may not accurately reflect the primary event of antigen-antibody binding. Of equal importance is the variation of results found with different substrates and techniques though these are now being standardized with the help of WHO. The ANA reaction is a screening test for many diseases and is not specific for SLE (with the exception of SM antibody). It does, however, allow the type of immunoglobulin involved to be determined and also whether it is complement fixing or not, which may be important for the prediction of renal involvement. He had found, using the counter immunoelectrophoresis (CIE) method for detection of anti-DNA antibodies, that the test tended to be positive in nonrenal forms of SLE. (Dr. Barnett suggested that if CIE is positive for ds-DNA the patient was very likely to have cerebral lupus.)

Patterns of staining carried some diagnostic significance; for example, the rim (or ring) staining patterns represented antibodies to ds-DNA and thus were more specific for SLE, but in their experience, a speckled pattern carried little diagnostic specificity. A granulocyte-specific ANA had been found in 20% of juvenile rheumatoid arthritis cases and in 60% of adult rheumatoid arthritis cases, and some sera also possessed an eosinophil-specific antibody. Granulocyte-specific ANA appeared to be related to a higher titre of Rose-Waaler tests and complement depletion in Felty’s syndrome. Their family studies had shown only a slightly higher incidence of ANA in the relatives of SLE patients.

An extensive literature has developed involving the clinical significance of antibodies to ds-DNA and ss-DNA. Dr. P. H. Schur (Harvard Medical School, Boston, Mass., USA) related his own extensive experience and reviewed the literature regarding different tests that recognize these antibodies. He dispelled the impression that antibodies to ds-DNA might indeed be specific for lupus and noted that although at least half of the patients with SLE have been found at some time or other to have antibodies to ds-DNA, the antibodies have also been found (by binding assays) in some normal individuals and in somewhat increased amounts in some patients with many different types of chronic rheumatic illnesses, in particular rheumatoid arthritis, juvenile rheumatoid arthritis, scleroderma, Sjogren’s syndrome, and chronic active hepatitis. Therefore, it was his feeling that although high titres usually indicated a diagnosis of SLE, their presence could not be used as a sine qua non for its diagnosis. However, given the presence of these antibodies in a patient with SLE, particularly when nephritis was present, increasing anti-DNA antibody titres, particularly in association with falling complement levels, indicated increasing activity and were a useful guide to therapy. The levels tended to return towards normal as the patient went into remission. Dr J. Holian (Radiochemical Centre, Amersham, England) discussed the problems of standardizing routine tests, and suggested improvements (Holian and others, 1975). It seemed obvious that the value of anti-DNA antibody estimations still requires further clarification and much of the problem lies in the variability of antigens, laboratory techniques, and indeed, the clinical definition and delineation of diseases under investigation.

Other factors may influence the disease pattern and Dr R. N. Maini (Kennedy Institute, London) discussed the technique of using antihuman immunoglobulin for precipitation of radiolabelled DNA bound to antibody, thus allowing the class of the antibody to be investigated (Glass and others, 1973). DNA antibodies belonging to IgG class were almost invariably present in sera showing any increased DNA binding; in only a third was IgM anti-DNA...
antibody detectable usually in significantly smaller amounts than IgG. In a few patients the IgM levels had been found to be equal to IgG antibody levels, and in this situation, central nervous system involvement was a clinical feature. Spontaneous precipitation of radiolabelled DNA was found in certain sera, particularly those with very large amounts of anti-DNA antibody or in association with IgM antibodies.

Maini reported that their group had also investigated avidity of anti-DNA antibodies (defined as the energy of association of antigen and antibody). Preliminary evidence indicated that low avidity was found in patients with renal involvement, whereas high avidity antibody occurred in nonrenal SLE (Steward and others, 1974). Thus far the avidity of serum antibodies had been measured but it may be more important to investigate the avidity of the tissue fixed antibody since this was more relevant to the pathogenesis of the disease. It is probable that antibody avidity could vary with the stage of the disease and preliminary results suggested the immunosuppressive treatment may increase the amount of low avidity antibody (this in itself might be a disadvantage were it to occur without a marked drop in the amount of antibody—perhaps the regulation of immunosuppressive therapy is to become even more difficult).

Dr. Eng M. Tan (Scripps Clinic and Research Foundation, La Jolla, Calif., USA) reviewed the occurrence of antibodies to non-DNA nuclear antigens, namely a glycoprotein (Sm) and a ribonucleoprotein (RNP). He presented evidence that the speckled pattern of immunofluorescence was produced by antibodies to either of these antigens. Antibody to RNP was found in very high titre in all cases of mixed connective tissue disease (Sharp and others, 1972) and was present in lower titres in SLE and other diseases such as scleroderma. On the other hand, antibody to the Sm antigen was found only in a proportion of patients with SLE and was very suggestive of being a specific marker for this disease (Notman, Kurata, and Tan, 1975). He had found raised ds-DNA binding in diseases other than SLE.

In summary, antibodies to nuclear antigens are not specific for a single disease but the particular profile of antibodies and their titres appeared to be of diagnostic significance.

The rest of the meeting was devoted to diseases other than SLE in which anti-nuclear antibodies occur. Dr. G. R. V. Hughes (Royal Postgraduate Medical School, London) discussed the significance of drug-induced ANA. Three main mechanisms were postulated: activation of a latent virus, chemical alteration of nuclear proteins, and a genetic diathesis. Pure ds-DNA is a poor antigen but immunogenicity could be markedly increased by ultraviolet irradiation (UV-DNA), or by linking to procainamide. Such a mechanism may be the method of production of the SLE-like syndrome found in patients taking procainamide. Hydralazine is known to combine with soluble nuclear protein but its immunological effects were not clear; in this group genetic factors may also be a factor since many of these patients have a defective acetyl transferase system with impairment of catabolism of hydralazine.

Drug-induced lupus syndromes are relatively rare, having about 1/10 the incidence of the classical SLE syndromes and differ from these in having no renal or neurological disease and rarely antibody to ds-DNA (with the exception of penicillamine-induced SLE). Persisting symptoms in a minority of drug-induced SLE cases suggests the existence of a latent SLE diathesis which has been triggered by the drug. It is possible that many cases are undiagnosed; for example, up to a third of patients on chlorpromazine develop ANA. However, since there are usually no associated clinical features, a positive antinuclear factor has to be distinguished from the clinical syndrome. Patients with drug-induced ANA can be divided into two categories.

(A) Patients receiving prolonged administration of drugs, e.g. anticonvulsant therapy, isoniazid, possibly chlorpromazine, and hydralazine. In animals studies, hydralazine linked to a protein such as human serum albumin resulted in antibody production only if given in repeated injections; the finding of ANA in subacute bacterial endocarditis may also be an example of chronic immunization.

(B) The second, and rarer, group are patients developing an acute lupus syndrome. Methyl dopa, methylothauracil, contraceptive therapy, and practolol (Eraldin) are included in this group. Much work has and is being centred on practolol-induced disease in which the process may continue after stopping the drug. In certain cases there is associated peritoneal fibrosis, alteration of the immune response (particularly depressed lymphocyte function), and increased DNA binding, which tends to be a little higher in patients whose clinical features include skin rashes.

Professor M. Turner Warwick (Cardiothoracic Institute, London) discussed the prevalence and the profile of ANA found in chest disease. Although cryptogenic fibrosing alveolitis can occur in association with recognized autoimmune diseases, it is often a solitary finding. ANA was found in 37% of patients, the incidence being the same in both types. ANA was found to fix complement in about a third of the cases. An increased prevalence of ANA was also found in certain forms of inorganic dust pneumoconiosis, for example, occurring in 25% of patients with radiographic asbestosis but not in workers with a similar exposure but with normal radiographs. A high incidence (44%) of ANA was
also found in sandblasters silicosis. There was a
general trend of increasing prevalence of ANA with
more advanced radiographic grades of inorganic
dust pneumoconiosis.

More detailed studies of the clinical features of
ANA positive patients show considerable differences
in different lung diseases. In asbestosis the ANA is
age related and the normal rise of ANA with age is
exaggerated; in contrast, in cryptogenic fibrosing
alveolitis the rise is equally marked in both young
and old. The DNA binding test is usually negative in
dust and cryptogenic disease and is positive in only
24% of cases of SLE presenting with pulmonary or
pleural involvement, although in the latter group a
higher incidence of positive DNA antibodies
measured by CIE tests were found (Holgate and
others, 1976). Continuing interest will obviously
centre on the different responses in the various
syndromes and the nature of the precipitating
factors in particular, the part played by exposure
to dust.

In his series of 300 cases of myasthenia gravis
(MG) Dr. T. E. W. Feltkamp (Plesmanlaan, Amsterdam,
Netherlands) had found 12 with rheumatoid
arthritis, 1 SLE and 2 with possible SLE, 18 with
hyperthyroidism, 4 with pure cell anaemia, and 1
Addison's disease. The frequency of ANA in MG
was very dependent on the nuclear substrate; with
one or more of seven distinct substrates a positive
ANA was noted in over 30%. In patients with MG
and a thymoma the frequency of positive ANA was
as high as 50% (the same frequency being found in
patients with a proven thymoma but without MG).
Whether part of this increased ANA in patients
with thymoma is due to the increased incidence of
SLE in these patients is uncertain, and reference was
made to various antibodies against muscle and
nerve antigens also found in MG and the evidence
for possible genetic factors in the younger patients
without thymoma in whom HLA-B9 occurred more
frequently.

Professor J. S. Cameron (Guy's Medical School,
London) discussed the value of antinuclear antibody
tests in renal lupus erythematosus. He has asked
the question whether the Farr test could be used to
separate the presumed soluble complex disease in
SLE nephritis from soluble complex disease occur-
ing in other forms of nephritis. In renal SLE he had
found high DNA binding even if the patient was
being very actively treated by 'immunosuppression',
wheras in other forms of glomerulonephritis, DNA
antibody levels fell within the normal range
indicating that the test was a good discriminant. In
following the progress of the renal lupus, regular
measurement of DNA antibodies and complement
are used by some laboratories to assess the disease
activity. Cameron had found that the best index of
the state of renal disease is the level of C4. In
addition, severe disease is usually associated with
high DNA antibody levels but the converse had not
been found to be true.

At a workshop held at the Kennedy Institute,
London, the following day, results of a laboratory
study on the measurement of anti-DNA antibodies
carried out by 12 laboratories in Europe and the
USA on the same sera provided an opportunity for
critical evaluation of a number of methods in
current use (Maini and Holborow, 1976). The study
has emphasized areas of disagreement on the
detection and quantitation of anti-ds (and ss)-DNA
antibodies, a finding which should cause some con-
cern to scientists and clinicians employing these
techniques. The need for further work in standard-
ization of reagents and materials and continued
exchange of information and co-operation has been
highlighted in this field.

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