Use of Laser Nephelometry in the Measurement of Serum Proteins

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Measurement of immunoglobulins (Ig) and of complement component C3 in human serum by automated and manual nephelometric techniques is tedious, and the effective linear range is too narrow. We describe a laser nephelometer/reagent system for measuring serum proteins by the use of forward light scatter (which enhances the ratio of reaction/blank), electronic blank subtraction, laser light (632 nm), and electronic signal selection. We report data establishing the range of linearity for immunoglobulins IgG, IgA, IgM, and complement C3 with this system, and correlations with results by a radial immunodiffusion. We also compared an electroimmunodiffusion system for quantitation of albumin and IgG in cerebrospinal fluid to our technique. The nephelometric system described provides a rapid, accurate, precise, and objective way to measure immunoglobulins and C3.

Additional Keyphrases: immunoglobulins • complement C3 • radial immunodiffusion • electroimmunodiffusion • percent relative light scatter • multiple sclerosis • cerebrospinal fluid

Measurement of immunological reactions by nephelometry has been a method in which light scatter was measured at an angle of 90° (1). For immunological applications this limits the sensitivity of the technique and does not allow sample background to be well differentiated from the specific immunological reaction being quantitated (2).

We have developed a nephelometer that incorporates a laser as the light source and an optical system that detects forward light scatter (3). Therefore, detection of light scatter from antigen/antibody complexes is improved. The amount of signal from artificial light scatter (dust and larger contaminating particles) is limited by an electronic screening device. By incorporating the principles of forward light scatter, we designed a cuvette chamber that accepts disposable round cuvettes, obviating problems and cost of a flow-through cuvette system or square cuvettes.

This instrument also has electronic memory capability that enables automatic subtraction of light-scatter readings attributable to the various blank constituents (buffer, antibody, and sample). The final digital readout of percentage relative light scatter is proportional to the amount of antigen/antibody complexes present in the sample test cuvette, which obviates the subjectivity of interpreting recorder traces and measuring precipitin zones. The use of a polymeric buffer in this system, which decreases the solubility of high-molecular-weight antibody/antigen complexes, has resulted in rapid measurement of serum proteins and an extended range of linearity. Therefore, it is possible to quantitate various concentrations of serum proteins without additional dilution or concentration of the specimen.

We describe here some of the applications of the laser nephelometer system for the quantitation of the immunoglobulins (IgA, IgG, and IgM), complement C3, and albumin.

Materials and Methods

Instrumentation

The Laser Nephelometer "PDQ" (Hyland Laboratories, Inc., Costa Mesa, Calif. 92626) contains a helium/neon laser light source emitting photons at 632.8 nm, a photomultiplier tube (No. 931B with an S-4 spectral response) mounted at an angle of detection of 31°, electronic blanking capabilities for each constituent (buffer, antiserum and sample), and a signal selector, which differentiates light scatter attributed to large contaminating particles.

Reagents

The "LAS-R" Nephelometric Reagent Test Kits (Hyland) for IgA, IgG, IgM, complement C3, and albumin were used in the nephelometric procedures. Each kit contains: monospecific goat antiserum diluted to cover an antigenic range from fourfold reference I to reference VI, a polymeric buffer (pH 7.0) at a concentration to produce precipitation of compounds of higher molecular weight than are normally present in serum or cerebrospinal fluid, and six multicomponent reference sera (pooled delipidized human sera).

The reference value ranges are: IgA, 24 to 740 mg/100 ml; IgG, 80 to 2700 mg/100 ml; IgM, 7.5 to 235 mg/100 ml; C3, 9.0 to 325 mg/100 ml; and albumin, 300 to 9420 mg/100 ml. The kit also contains disposable 10 × 75 mm borosilicate cuvettes.

"Immunoplate" III Radial Immunodiffusion Test Kit for IgA, IgG, IgM, complement C3, and cerebrospinal fluid, albumin, and IgG (Hyland) were used to obtain results by radial immunodiffusion. The IgG and IgM plates contained goat antiserum; the IgA and C3 plates used contained horse antiserum. The three references supplied were prepared for a human serum pool.
Different saline, 0.1 ml of distilled water, and 0.4 ml of saline, were used to filter the nephelometric reagents.

Electroimmunodiffusion plates were prepared (4) and "LAS-R" kit references II, III, and IV (Hyland) were used to establish a reference curve.

A Precision Viewer (Hyland) was used to determine radial immunodiffusion zone diameters to the nearest 0.1 mm.

Specimens

Serum specimens were collected from 60 apparently healthy individuals, 18 to 60 years of age. Serum specimens were obtained from patients with diagnosed IgA, IgG, and IgM monoclonal gammopathies. "Low level" sera were collected from patients with various diagnosed immunological deficiencies that would be expected to result in decreased concentrations of the protein being assayed. Cerebrospinal fluid specimens were collected from patients with normal concentrations of IgG and albumin. Abnormal cerebrospinal fluid specimens were obtained from patients with multiple sclerosis.

Blind samples used in our precision study were from a pool of delipidized and lyophilized human serum. Five different concentrations of protein were obtained by reconstituting each vial with distilled water or water and saline, as follows:

1. 0.3 ml of distilled water
2. 0.5 ml of distilled water
3. 1.0 ml of distilled water
4. 1.0 ml of distilled water plus 1.0 ml of saline (9 g of NaCl per liter)
5. 1.0 ml of distilled water plus 2.0 ml of saline (9 g of NaCl per liter)

Reconstituted vials were stored refrigerated (5 °C) until assayed. All other specimens were stored frozen (−20 °C) unless otherwise noted.

Procedures

Nephelometry. For nephelometry, we diluted the various "LAS-R" kit antisera twofold with polymeric buffer. The working antiserum was filtered through a 0.4 µm (av pore diameter) × 47 mm filter, to remove particulates. Saline was filtered in the same manner. For each assay system, to a duplicate series of 10 × 75 mm disposable cuvettes (for each reference and unknown), 1 ml of the working antiserum was added and labeled sample test. To a separate series of cuvettes (for each reference and unknown blank) 1 ml of the previously filtered saline was added. A saline blank and antiserum blank cuvette were prepared by pipetting into the cuvettes 1 ml of saline and antiserum, respectively. The nephelometer kit references and unknown specimens were diluted 100-fold with the filtered saline, except for cerebrospinal fluid specimens, which were assayed undiluted. Reference and specimen dilutions were pipetted into the sample blank and test cuvettes (25 µl for IgA and IgG, 100 µl for IgM and complement C3, and 5 µl for albumin). The cuvettes were sealed, their contents mixed by inverting twice, and incubated for 1 h at room temperature (25 °C), except for cerebrospinal fluid assay tubes, which were incubated for 30 min. We measured the percentage relative light scatter from these cuvettes by placing the saline blank cuvette into the cuvette well and "zeroing" the nephelometer in the buffer position, with the photometer "blank-subtract" knob. The reference cuvette with the highest concentration of reactants was then placed in the instrument and the upper reference point established by adjusting the sensitivity (coarse and fine) to obtain a value of about 180% relative light scatter. The instrument mode was switched to "antiserum blank" and the antiserum blank cuvette was placed into the well. The compute cycle was activated by pressing the "compute" button. At the end of a 15-s compute cycle the percentage relative light scatter from the antiserum blank was subtracted from the results by adjusting the "antiserum blank" knob. The "sample blank" mode was activated by placing reference I into the instrument, and the compute cycle was activated. The percentage relative light scatter attributed to the sample blank was automatically removed. The reference I test cuvette was placed in the instrument and read by pressing the "test" mode button. The displayed percentage relative light scatter was recorded. The other sample blanks and tests were read in the same way. The displayed values are proportional to the concentration of the antigen concentration within the sample. These values for the references were plotted on linear graph paper vs. the listed mg/100 ml, and a line of best-fit was drawn connecting the points. The values for the unknown samples were read from this curve and converted to mg/100 ml.

The nephelometer kit reference I was diluted 12.5-fold with saline, producing a concentration eightfold the normal (100-fold) reference I concentration. Lower reference concentrations were made by serial twofold dilutions of the above reference dilution to 8192-fold (resulting in 14 different concentrations). These dilutions were assayed by the above procedure for each antigen—IgA, IgG, IgM, and complement C3—to determine the range of linearity of the antiserum.

Nephelometry assays were conducted on the previously collected normal, subnormal, and supranormal sera specimens by the above procedure, and for these results we calculated correlations with results by radial immunodiffusion and electroimmunodiffusion. Specimens with antigen concentrations above reference I were diluted further than 100-fold and reassayed until two consecutive dilutions resulted in values for percentage relative light scatter that were on the reference curve. Sera with concentrations below reference VI were only diluted 10-fold with saline and re-assayed to obtain values that fell on the reference curve. We assessed precision by assaying the previously prepared lyophilized blind samples, within-run by 20 assays of each concentration of blind sample, with use of a duplicate series of references, and day-to-day assays by reconstituting the various concentrations of blind samples and assaying them on each of several days.

Radial Immunodiffusion

We used an end-point radial immunodiffusion system to quantitate serum IgA, IgG, IgM, and C3, and cerebrospinal fluid IgG and albumin in the previously described normal and abnormal specimens. Nephelometry references II, III, and IV were used with this system; the squares of zone diameters were plotted vs. concentration on linear graph paper, and the best-fit curve was drawn. Specimens with above-normal concentrations were appropriately diluted with saline so that zone diameters fell within the range of the reference curve. Cerebrospinal fluid assays were done by diluting nephelometric references 100-fold in saline, but assaying the cerebrospinal fluid undiluted.

Electroimmunodiffusion

Electroimmunodiffusion plates were prepared according to a modified Laurell technique (4). Nephelometer references II, III, and IV were diluted 100-fold with saline and the appropriate values assigned. Reference precipitin cone lengths were plotted on log-log graph paper and a curve of best-fit was drawn along these points. Values for albumin and IgG in cerebrospinal fluid from patients with multiple sclerosis were obtained from this reference curve. Samples with precipitin cones larger than that of reference II were diluted with saline and re-assayed.

Results

The range of linearity for the nephelometric reagents was determined by plotting, on linear graph paper, percentage relative light scatter of a series of reference dilutions vs. representative concentrations for IgG. Owing to the extended range of concentrations, multi-

![Fig. 1. IgG linearity on instrument sensitivity 1 (3000–24000 mg/100 ml)](image1)

graphs of the data obtained at the various instrument sensitivities were used to demonstrate the linearity of the curve. The upper reference concentrations were read by using instrument sensitivity setting No. 1. IgG concentrations that exceeded about 9000 mg/100 ml were in antigen excess (Figure 1). Below this value the relationship was curvilinear. To expand the lower reference curve, the instrument sensitivity switch was adjusted to No. 2 for the 188–3000 mg/100 ml range (Figure 2), to No. 5 for the 3–94 mg/100 ml concentration (Figure 3).

The total range of curvilinearity for the IgG antiserum was observed to be from 3 to about 9000 mg/100 ml. Similar assays were conducted for IgA, IgM, and C3, with the following results: IgA, 21–2800 mg/100 ml; IgM, 7–1200 mg/100 ml; and C3, 8–1200 mg/100 ml.

We did nephelometric and radial immunodiffusion assays of sera from 70 normal and IgA-deficient sera as well as sera from patients with IgA gammopathies. A correlation coefficient of 0.960 was obtained. Figure 4 shows the results. The radial immunodiffusion technique gave slightly higher values for the IgA myeloma samples than those obtained by nephelometry (slope, 1.192). To observe the correlation from specimens with "normal" antigenic characteristics, we constructed a scatter graph for results from the normal and deficient samples, omitting the elevated; the slope decreased to 1.06 (Figure 5).

Sixty-nine sera from normal, deficient, and patients with IgG gammopathies were assayed for IgG by using both nephelometry and radial immunodiffusion. The correlation coefficient was 0.988, the slope 0.984. A scatter graph (Figure 6) shows these results. Again, when the results from the paraproteinemias were excluded, the slope was 1.039. Similar assays with IgM
gave correlation coefficients of 0.985 and a slope of 1.697 (Figure 7).

As previously explained, by excluding the results from IgM myelomas, the slope changes to 0.814 (Figure 8), which again indicates that higher readings were obtained by radial immunodiffusion than by nephelometry for paraproteinemia specimens. Complement C3 assays on 90 samples gave a correlation coefficient of 0.9696, with a slope of 1.181 (Figure 9).

Three groups of specimens, consisting of 60 normal sera, were assayed by three individual laboratories by the nephelometric technique. Table 1 lists the values and range (±2 SD) for each protein specificity. A series of blind samples at different concentrations, prepared from a pool of normal human serum, was assayed by nephelometry for IgA, IgG, IgM, and C3. Run 1 consisted of a single run of 20 replicate assays of each concentration, to ascertain within-run precision. Run 2 consisted of 55 assays of each of the freshly reconstituted and diluted blind samples, for day-to-day precision. Table 2 shows the results.

Table 3 lists albumin and IgG values determined by nephelometry and radial immunodiffusion for 12 normal samples of cerebrospinal fluid. Nine individual specimens and one pool of cerebrospinal fluid from patients with multiple sclerosis were also assayed for...
these proteins by nephelometry and electroimmunodiffusion (Table 4).

**Discussion**

Molecular light scattering has been used to estimate the molecular weights of biological materials (5) and to detect antigens by immunological reactions (6). Nephelometric techniques in which 90° light scatter is measured have been used to quantitate proteins in serum and cerebrospinal fluid (7, 8). However, it has been known for some time that it is possible to detect greater total light scatter by observing the scatter at a forward angle (9, 10). The advantages obtained in doing so include increased sensitivity and an increased difference between the sample blank and immunological reaction in percentage relative light scatter ratios. With these advantages in mind, we have developed a nephelometer that measures forward light scatter, for enhanced detection of antigen/antibody complexes. This nephelometer includes a laser, which provides an intense source of illumination that is highly collimated and coherent. The reagent system used with this instrument incorporates a polymeric buffer, which enhances the insolubilization of antigen/antibody com-

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Table 1. Results for Assay of Normal Serum by Three Individual Laboratories (n = 60/Laboratory)

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<th>Laboratory</th>
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<tr>
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<td>153</td>
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<tr>
<td>2</td>
<td>159</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
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</table>

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Fig. 9. Nephelometry and radial immunodiffusion assay compared, for 90 samples with deficient and normal concentrations of complement C3
plexes, in turn increasing light scatter and detectability within relatively short incubation times. Clearly, laser nephelometry is a sensitive, precise, and accurate technique for quantitating proteins in human serum and cerebrospinal fluid. The results obtained from the linearity studies demonstrate the versatility of this procedure.

A potential problem in serum immunoglobulin measurement is the formation of soluble immune complexes in the presence of antigen excess. Therefore, samples with extremely above-normal concentrations of antigen must be diluted and re-assayed until linearity with dilution can be established within the range of the reference curve. However, the quantitation of myeloma proteins is subject to error because of the unique antigenic mosaic of these proteins, the method of standardization, and the nature of the immunizing antigen. The correlation studies show that samples with extremely supranormal amounts of antigen must be diluted for measurement by radial immunodiffusion, which may alter the diffusion characteristics of these proteins in agar gel.

When normal sera were assayed by three separate laboratories by laser nephelometry, there were only slight differences in the mean values. The coefficients of variation for the five concentrations of pooled sera were relatively constant in magnitude, indicating antigen concentration not to be a source of substantive variance. The panel of normal cerebrospinal fluid specimens assayed for IgG by nephelometry and radial immunodiffusion gave means of 1.5 and 2.2 mg/100 ml, respectively. The albumin assays for the same systems gave values of 16.9 and 15.1 mg/100 ml. For IgG in cerebrospinal fluid from patients with multiple sclerosis we found mean values of 10.8 mg/100 ml by the nephelometric method, 12.5 mg/100 ml by electroimmuno-diffusion. Values for albumin were 34.8 and 35.1 mg/100 ml, respectively, for these same samples.

### Table 2. Within-Run and Day-to-Day Precision for Nephelometry of IgA, IgG, IgM, and Complement C3

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>IgA Mean, mg/100 ml</th>
<th>CV, %</th>
<th>IgG Mean, mg/100 ml</th>
<th>CV, %</th>
<th>IgM Mean, mg/100 ml</th>
<th>CV, %</th>
<th>C3 Mean, mg/100 ml</th>
<th>CV, %</th>
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<td>Within-run (n = 20)</td>
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### Table 3. IgG and Albumin in 12 Normal Human Cerebrospinal Fluids, as Measured by Radial Immunodiffusion and Nephelometry

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<th>RID</th>
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### Table 4. IgG and Albumin in Cerebrospinal Fluid from Patients with Multiple Sclerosis, as Measured by Electroimmunodiffusion and Nephelometry

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*a Treated multiple sclerosis.

b Poor.

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As indicated from the results, laser nephelometry provided acceptable correlation with the various comparison methods, but had the advantage of an extended range.

Precision was acceptable for the various protein specificities and concentrations assayed. Hence, we believe the laser nephelometric system offers the clinical laboratory a rapid, precise, objective means to assess proteins in sera and cerebrospinal fluid.

We thank Dr. Wallace W. Tourtellotte and staff for electroimmunodiffusion studies performed in his laboratory, Mr. Gregory Bateman and Mr. Robert Hughes for technical assistance, and Dr. Michael Caputo for clinical results.

References