1) Paraproteins:
   a. Definition: Monoclonal immunoglobulins or portions of immunoglobulins produced by a neoplastic proliferation of antibody producing cells
   b. Methods of detection: Protein electrophoresis and Immunofixation
   c. Multiple myeloma as the prototype paraprotein disease
      i. Criteria for diagnosis of myeloma
      ii. Kidney in multiple myeloma
         1. Proteinuria (~90% of patients)
         2. Bence-Jones proteinuria (~50% of patients)
         3. Renal insufficiency (> 50% of patients)
         4. Autopsy findings
            a. Cast nephropathy (30-50%)
            b. Primary AL-amyloidosis (~10%)
            c. Light chain deposition disease (~5%)
   d. Patterns of renal deposition determine clinical presentation (bulleted/bolded disease entities associated with each pattern are the main topics of this presentation):
      i. Isolated light chain deposition in glomerular basement membranes causes proteinuria or nephrotic syndrome
         • Kappa light chain nephropathy
         • Amyloid nephropathy
      ii. Light chain accumulation in proximal tubular epithelial cells causes cellular dysfunction and activation of cytokine-producing pro-inflammatory phenotype
         • Fanconi syndrome
         • Chronic interstitial nephritis
      iii. Light chain deposition occluding tubular lumens causes acute renal failure
         • Myeloma cast nephropathy
      iv. Whole immunoglobulin deposition in glomeruli causes combined hematuric and proteinuric syndromes (nephritic/nephrotic)
         • Cryoglobulinemia
         • Immunotactoid glomerulopathy
   e. “Paraprotein related diseases”
      i. Not all amyloid, immunotactoid or cryoglobulin deposits are composed of paraprotein. These broader topics will be elaborated.
      ii. Not all Fanconi syndrome or chronic interstitial nephritis cases are due to paraprotein accumulation. The causes of these patterns of injury are beyond the scope of this presentation.

2) Specific types of paraproteins produce distinctive patterns of deposition.
   a. Injecting human Bence-Jones proteins into mice reproduce the specific patterns of cast formation, basement membrane deposition or fibril formation that was present in the patients from who the proteins were harvested [NEJM 324(26): 1845, 1991]
   b. Molecular features of the paraprotein correlate with patterns of deposition
      i. Light chains causing cast nephropathy have propensity to bind Tamm Horsfall protein
      ii. Amyloid is mostly λ (V₆); when κ usually limited to
      iii. Kappa light chain nephropathy usually Vk1 or Vk4
      iv. Fanconi syndrome almost invariably Vk1 with specific amino acid substitution causing incomplete catabolism (protease resistance)
3) Immunotactoid (Fibrillary and Microtubular) glomerulopathies

Development of knowledge
1977 - Congo red-negative, “amyloid-like” fibrillary deposits with IgG and C3
1980 - Parallel microtubular arrays containing Ig and C3 (“immunotactoid”)
1990s – Controversy over nomenclature

<table>
<thead>
<tr>
<th>Congo Red</th>
<th>AL-Amyloid</th>
<th>Fibrillary-type Immunotactoid</th>
<th>Microtubular-type Immunotactoid</th>
<th>Light chain nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Fibril diameter &amp; configuration</td>
<td>10 nm Random</td>
<td>20 nm Random</td>
<td>&gt; 30 nm Parallel arrays</td>
<td>Dense granules No fibrils</td>
</tr>
<tr>
<td>Fibril composition</td>
<td>Monoclonal Ig light chains (usually lambda)</td>
<td>Whole Ig, usually polyclonal with component of IgG₄</td>
<td>Whole Ig, often monoclonal</td>
<td>Monoclonal Ig light chains (usually Kappa)</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>Plasma cell dyscrasia</td>
<td></td>
<td>Hematologic malignancy</td>
<td>Plasma cell dyscrasia</td>
</tr>
<tr>
<td>Systemic deposition</td>
<td>Yes</td>
<td>Rare reports</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

4) Cryoglobulinemia

Development of knowledge and Classification
1933 Cryoprecipitates in a patient with multiple myeloma
1947 Purpura with “cryoglobulins” (immunoglobulins that precipitate in cooled serum and re-dissolve on heating)
1966 Cryoglobulinemia clinical syndrome: purpura, arthralgia, weakness and renal disease
Characterization of the cryoprecipitates and identification of rheumatoid factor activity
1974 Brouet Classification

<table>
<thead>
<tr>
<th>Type I</th>
<th>Components of cryoprecipitate</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monoclonal immunoglobulin</td>
<td>Waldenstrom’s macroglobulinemia or multiple myeloma</td>
</tr>
<tr>
<td>Type II</td>
<td>Monoclonal rheumatoid factor (usually IgM kappa) and polyclonal immunoglobulin</td>
<td>Hepatitis C virus infection</td>
</tr>
<tr>
<td>Type III</td>
<td>Polyclonal immunoglobulin with antiglobulin activity against polyclonal immunoglobulin of a different isotype</td>
<td>Various autoimmune and inflammatory disorders</td>
</tr>
</tbody>
</table>

1992 Role of Hepatitis C virus in type II (“essential mixed”) cryoglobulinemia [NEJM 327: 1490]

Pathology associated with cryoglobulinemia:
- Systemic immune complex small vessel vasculitis
- MPGN with cryothrombi occluding arterioles and glomerular capillaries