The Monoclonal Gammopathies

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Each monoclonal protein (M-protein, or myeloma protein) consists of two heavy polypeptide chains of the same class and subclass and two light polypeptide chains of the same type. Electrophoresis on cellulose acetate membranes is satisfactory for screening, although agarose electrophoresis is more sensitive for detecting small M-proteins. Immuno-electrophoresis should be performed when myeloma, macroglobulinemia, amyloidosis, or a related disorder is suspected. Immunofixation is useful when results of immuno-electrophoresis are equivocal. The recognition of a Bence Jones protein depends on the demonstration of a monoclonal light chain by immuno-electrophoresis or immunofixation of an adequately concentrated urine specimen. The differential diagnosis of an M-protein includes monoclonal gammopathy of undetermined significance (benign monoclonal gammopathy), multiple myeloma, solitary plasmacytoma of bone or extramedullary plasmacytoma, macroglobulinemia, lymphoma, chronic lymphocytic leukemia, and primary systemic amyloidosis.

Indexing Terms: amyloidosis/electrophoresis/immuno-electrophoresis/immunofixation/proteins/chemotherapy/immunoglobulins/heavy-chain disease/Bence Jones protein/multiple myeloma

Monoclonal proteins (M-proteins or myeloma proteins) are individual antibodies produced by plasma cells arising from a single clone of cells. Each M-protein consists of two heavy polypeptide chains of the same class and subclass and two light polypeptide chains of the same type (1). Different kinds of M-proteins are designated by capital letters that correspond to the class of their heavy chains, which are designated by Greek letters: IgG (γ in immunoglobulin G), IgA (α in immunoglobulin A), IgM (μ in immunoglobulin M), IgD (δ in immunoglobulin D), and IgE (ε in immunoglobulin E). The subclasses are IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2; their light-chain types are kappa (κ) or lambda (λ).

Although M-proteins appear to be abnormal, they actually represent excessive quantities of immunoglobulins that occur normally. The striking feature that led investigators to consider M-proteins abnormal is their homogeneity. In normal individuals, IgG is distributed from the α2 to the slow γ regions, but IgG monoclonal proteins are localized sharply in their electrophoretic migration. Each heavy-chain subclass and light-chain type of an M-protein has its counterpart among normal immunoglobulins and also among antigen-specific antibodies (2).

Monoclonal antibody activity in humans has been associated with a wide variety of bacterial antigens, including streptolysin O, staphylococcal protein, Klebsiella polysaccharides, and Brucella. However, the antigen for most M-proteins is not recognized, although it has been postulated that all M-proteins may have antibody activity (3). If a single clone is stimulated and escapes the normal controls over its multiplication, it reproduces excessively and synthesizes an excess of protein with a single heavy-chain class and subclass and a single light-chain type. Experiments with antisera to light chains showed that nearly all individual plasma cells contained κ or λ light chains but not both.

In some instances, heavy chains are not produced by the plasma cell, and only excessive quantities of light chains are detected. This condition has been designated "light-chain disease." A small proportion of myeloma cells, called "nonsecretory," do not secrete either heavy chains or light chains in detectable amounts because of either a simple failure of synthesis or a blocking of secretion. This lack of secretion occurs in only 1% of patients with multiple myeloma. In the heavy-chain diseases, portions of the heavy chains of IgG, IgA, or IgM are present in serum or urine.

Analysis of Serum for Protein

Procedures

Electrophoresis. Serum proteins should be analyzed by electrophoresis when multiple myeloma (MM), macroglobulinemia, or amyloidosis is suspected. Electrophoresis is also indicated in any patient with unexplained weakness or fatigue, anemia, increased erythrocyte sedimentation rate, back pain, osteoporosis or osteolytic lesions or fracture, immunoglobulin deficiency, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections (4). Serum protein electrophoresis should also be performed for any adult older than 30 years who has nephrotic syndrome, refractory congestive heart failure, orthostatic hypotension, peripheral neuropathy, or carpal tunnel syndrome; in such cases, a localized band or spike strongly suggests primary amyloidosis.

An M-protein (an excess of a single heavy-chain class and single light-chain type) usually is seen as a narrow peak (like a church spire) in the γ, β, or α2 regions of the densitometer tracing or as a dense, discrete band on the cellulose acetate membrane after electrophoresis (Fig. 1). In contrast, an excess of polyclonal immunoglobulins (having one or more heavy-chain types with κ and λ light chains) makes a broad-based peak or broad band and usually is limited to the γ region. Agarose electrophoresis is more sensitive than cellulose electrophoresis.

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1 Nonstandard abbreviations: M-protein, monoclonal protein; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma; and HCD, heavy-chain disease.

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A patient can have an M-protein even when the total protein concentration, $\beta$- and $\gamma$-globulin values, and quantitative immunoglobulin results are all within normal limits. A small monoclonal peak may be concealed among the $\beta$ or $\gamma$ components and therefore be overlooked. Indeed, the cellulose acetate pattern and densitometer tracing may appear normal even when an M-protein is present (Fig. 2). In such cases, immunoelectrophoresis or immunofixation is required for identification (5). A monoclonal light chain (Bence Jones proteinemia) is rarely seen on the cellulose acetate tracing. In IgD myeloma, the M-protein appears small or is not evident at all. Often, the M-protein is not apparent in the heavy-chain diseases.

**Immunoelectrophoresis.** Immunoelectrophoresis is useful for identifying an M-protein; it should be performed when a sharp peak or band is found in the cellulose acetate tracing or when MM, macroglobulinemia, amyloidosis, or a related disorder is suspected—even in the setting of a normal electrophoretic pattern, as was shown in Fig. 2. Because the antigenic determinants of some M-proteins are so restricted that they may not be recognized by all antisera, it is always helpful to use antisera from various sources.

In MM, monospecific antisera to IgG, IgA, IgD, or IgE, or to $\kappa$ or $\lambda$, produce a localized thickening or bowing of a heavy-chain arc and a similar thickening or bowing of a light-chain arc. Alterations in the heavy-chain and light-chain arcs should be about the same distance from the well. Occasionally, a thickened arc appears to be cut off abruptly near the trough. This may be due to antigen excess or to formation of a soluble antigen—antibody complex. In this situation, the immunoelectrophoresis should be repeated with serum diluted 1:5 or 1:10. The presence of an additional light-chain arc (double bowing) without a similar bowing of a heavy-chain arc indicates a free monoclonal light chain (Bence Jones proteinemia). However, the apparent free light chain may actually represent a component of a biclonal gammopathy or may actually be part of a monoclonal IgD or IgE M-protein.

We screen all sera for the possibility of an IgD or IgE M-protein. This screening is absolutely essential when bowing of the $\kappa$ or $\lambda$ arc is seen without an accompanying abnormality of an IgG, IgA, or IgM arc. Sera of patients can be ecologically screened by immunodiffusion by using antisera to IgD and IgE for each sample. All sera forming a precipitin band are then subjected to immunoelectrophoresis with monospecific antisera to IgD, IgE, $\kappa$, and $\lambda$ chains. Most sera produce no reaction on immunodiffusion, making immunoelectrophoresis unnecessary.

**Immunofixation.** Immunofixation is useful when results of immunoelectrophoresis are equivocal or negative. In fact, many laboratories prefer to perform immunofixation instead of immunoelectrophoresis. A sharp, well-defined band of a single heavy-chain class and light-chain type is seen as an M-protein (6) (Fig. 3).
Immunofixation is helpful when one suspects an M-protein and finds only bowing of a single heavy chain or a single light chain on immunoelectrophoresis, especially in cases of an IgM M-protein, when bowing of the light chain is not apparent on immunoelectrophoresis. Immunofixation is also helpful in detecting a small M-protein in the presence of normal background immunoglobulins. It is particularly advantageous for the detection of a small M-protein in suspected myeloidosis, successfully treated myeloma, presence of a solitary plasmacytoma, or recognition of biclonal gammapathy.

Despite the obvious advantages of immunofixation, immunoelectrophoresis is useful as an initial procedure because it is technically easy and (in our laboratory) less expensive, and the results are generally satisfactory. In one report, immunofixation detected M-proteins in 15 cases when immunoelectrophoresis failed to recognize them (7). However, interpretation of immunofixation may also be misleading, and one can overdiagnose or underdiagnose patients with M-proteins depending on the dilution of the specimen.

A rate nephelometer based on the use of monospecific anti-κ and anti-λ antisera to identify the light-chain component may be used to detect large M-proteins in patients with suspected monoclonal gammapathy. However, in such tests, small M-proteins will have a normal κ:λ ratio and, consequently, will not be recognized. This is particularly so for patients with a small IgG κ M-protein. In a series of 336 serum samples, 88% were diagnosed after high-resolution electrophoresis, quantitation of immunoglobulins, and the κ:λ ratio; 12% required immunofixation for identification (8).

Quantitation of immunoglobulins. Quantitation of immunoglobulins is more useful than immunoelectrophoresis or immunofixation for detecting hypogammaglobulinemia. Radial immunodiffusion may be used for quantitation, but it is not recommended. The rate nephelometer is best for measurement of the immunoglobulins. Being unaffected by molecular size of the antigen, the nephelometric technique measures 7S IgM, polymers of IgA, or aggregates of IgG accurately. However, the concentrations of IgM may be 10 to 20 g/L greater than expected on the basis of the densitometric tracing. The IgG and IgA concentrations may also be spuriously elevated. The reason for this is not known (9).

Measuring serum viscosity. Serum viscosity should be measured when the IgM is > 30 g/L or the IgA or IgG is > 40 g/L; it should also be done in any patient with oronasal bleeding, blurred vision, or neurologic symptoms suggestive of a hyperviscosity syndrome. The Ostwald-100 viscometer (Fisher Scientific, Itasca, IL) is satisfactory for this purpose, but a Wells–Brookfield viscometer (Brookfield Engineering Labs., Stoughton, MA) is preferred because it is more accurate, requires less serum (~1.0 mL), and can perform at different shear rates and temperatures.

Thermal-Sensitive Proteins

Cryoglobulins. The serum must be evaluated for the presence of cryoglobulins—proteins that precipitate when cooled and dissolve when heated—if the patient has any symptoms or findings of vasculitis or other features of cryoglobulinemia. Cryoglobulins may be classified as follows: type I (monoclonal—IgG, IgM, IgA, or, rarely, monoclonal light chains), type II (mixed—two or more immunoglobulins, one of which is monoclonal), and type III (polyclonal—no M-protein is found) (10).

Unexpectedly, many patients with large amounts of cryoglobulin are completely asymptomatic, whereas others with small monoclonal cryoglobulins in the range of 10–20 g/L have pain, purpura, Raynaud phenomenon, cyanosis, and even ulceration and sloughing of skin and subcutaneous tissues upon exposure to the cold. The temperature at which the cryoglobulin precipitates is much more important than the amount of protein involved.

Most commonly, mixed cryoglobulins (type II) consist of IgM–IgG, but IgG–IgG and IgA–IgG combinations have been reported (10). Usually the quantity of the "precipitating protein" is < 2 g/L, and the precipitate may not reach maximal amounts for 7 days after collection and refrigerated storage; the serum protein electrophoretic pattern usually indicates normality or diffuse hypergammaglobulinemia. Patients with mixed cryoglobulinemia frequently have vasculitis, glomerulonephritis, lymphoproliferative disease, or chronic infectious processes. Hepatic dysfunction and serologic evidence of previous infection with hepatitis B virus are common in some series (11). More recently, hepatitis C has been associated with mixed cryoglobulinemia (type II) (12).

Pyroglobulins. Pyroglobulins precipitate when heated to 56°C and do not dissolve when cooled. Pyroglobulinemia is associated with MM (13) or macroglobulinemia (14). Pyroglobulins are asymptomatic and of no clinical consequence.

Analysis of Urine for Protein

Analysis of urine is essential in studying patients who have gammapathies. Dipstick tests are used in many laboratories to screen for protein, but these are often insensitive to Bence Jones protein and should not be used for this. Sulfosalicylic acid or Exton's test is more reliable for the detection of protein. Urinary protein may be quantified by using trichloroacetic acid precipitation, biuret reagent, or dye binding (5).

Screening tests for detecting Bence Jones proteins have been in use since discovery of the unique thermal properties of these proteins, but both false-positive and false-negative reactions occur. The heat test for Bence Jones proteins cannot be recommended. Recognition of Bence Jones proteinuria depends on the demonstration of a monoclonal light chain by immunoelectrophoresis or immunofixation of an adequately concentrated urine specimen.

Electrophoresis and immunoelectrophoresis. For all patients demonstrating a serum M-protein, electrophoresis and immunoelectrophoresis of urine should be performed. Both tests should also be done in all cases of MM, Waldenström macroglobulinemia, amyloidosis, monoclonal gammapathy of undetermined significance.
(MGUS), heavy-chain diseases, or suspicion of these conditions. Immunofixation of urine should also be done in evaluation of older patients with an "idiopathic" nephrotic syndrome; the presence of a light chain in this setting indicates primary amyloidosis or light-chain deposition disease (15).

A 24-h collection of urine must be obtained for determination of the total amount of protein excreted each day. This test is important when following the course of a patient with a monoclonal light chain because the amount of protein excreted correlates directly with the size of the plasma cell burden.

A urine M-protein is seen as a dense, localized band on the cellulose acetate electrophoresis strip or a tall, narrow, homogeneous peak on the densitometer tracing (Fig. 4). Occasionally, two discrete globulin bands may be seen in the cellulose acetate electropherogram of the urine. These bands may be a monoclonal light chain plus a monoclonal immunoglobulin fragment from the serum, or they may represent monomers and dimers of the monoclonal light chain. Rarely, two monoclonal light chains (k and l) (biclonal gammapathy) have been noted in the urine. A polyclonal increase of light chains is seen as a broad band extending through most of the y region. It is not unusual for a urine to give a negative reaction for protein and yet immunoelectrophoresis of the concentrated urine reveals a monoclonal light chain.

Theoretically, antisera that recognize only free k or l should be used rather than light-chain antisera that recognize light chains that are either free or part of an intact immunoglobulin. However, the former antisera are often either nonspecific or not potent enough, and a patient may have an immunoglobulin fragment that antisera to free k or l would not recognize. Consequently, it is advisable to use k and l antisera that are nonspecific and potent and recognize both free and combined light chains. If electrophoresis of the urine reveals a localized globulin spike, and immunoelectrophoresis does not demonstrate a monoclonal light chain, one must suspect the presence of y heavy-chain disease (HCD). Immunoelectrophoresis should then be done with antisera to IgG (y heavy chains).

**Immunofixation.** Immunofixation, which is more sensitive than immunoelectrophoresis, may be helpful in detecting monoclonal light chains. Immunofixation is most helpful when a monoclonal light chain occurs in the presence of a polyclonal increase in light chains. It is also useful in detecting monoclonal heavy-chain fragments in urine (Fig. 5).

**Differential Diagnosis of Monoclonal Gammapathies**

The monoclonal gammapathies may be classified as follows:

I) **MGUS**
   A. Benign (IgG, IgA, IgD, IgM, and, rarely, free light chains)
   B. Associated with neoplasms of cell types not known to produce M-proteins
   C. Bicalonal gammapathies

II) **Malignant monoclonal gammapathies**
   A. MM (IgG, IgA, IgD, IgE, and free light chains)
      1. MM
      2. Smoldering multiple myeloma (SMM)
      3. Plasma cell leukemia
      4. Nonsecretory myeloma
      5. Osteosclerotic myeloma (POEMS; polynuropathy, organomegaly, endocrinopathy, M-protein, skin changes)
   B. Plasmacytoma
      1. Solitary plasmacytoma of bone
      2. Extramedullary plasmacytoma
   C. Malignant lymphoproliferative disease
      1. Waldenström macroglobulinemia (primary macroglobulinemia)
      2. Malignant lymphoma
   D. Heavy-chain diseases
      1. y HCD
      2. a HCD
      3. µ HCD

![Fig. 4. Urine M-protein: (top) densitometric pattern showing a tall, narrow-based peak of β-mobility; (bottom) cellulose acetate electrophoretic pattern showing a dense band of β mobility consistent with a urine M-protein (Bence Jones protein). Source: Kyle RA, Garton JP. Laboratory monitoring of myeloma proteins. Semin Oncol 1986;13:310–7. Reprinted by permission of Grune & Stratton.](image)

![Fig. 5. Immunofixation of urine from patient with monoclonal λ protein plus an IgA λ fragment: (top) narrow, localized band with IgA (α) antisera; (middle) no reaction with λ antisera; (bottom) two discrete bands with λ antisera. Source: Kyle RA, Garton JP. Laboratory monitoring of myeloma proteins. Semin Oncol 1986;13:310–7. Reprinted by permission of Grune & Stratton.](image)
E. Amyloidosis

1. Primary
2. With myeloma
   (Secondary, localized, and familial amyloidosis have no M-protein)

MGUS (Benign Monoclonal Gammopathy)

The term monoclonal gammopathy of undetermined significance denotes the presence of an M-protein in persons without evidence of myeloma, macroglobulinemia, amyloidosis, or other related diseases. "Benign monoclonal gammopathy" is misleading because one does not know at the time of recognition of an apparently benign M-protein whether it will remain stable or will develop into symptomatic MM, macroglobulinemia or related lymphoproliferative disorders, or amyloidosis.

MGUS may be defined as an M-protein concentration <30 g/L; <10% plasma cells in the bone marrow; no or a small amount of M-protein in the urine; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency; and, most importantly, stability of the M-protein and failure of development of other abnormalities during long-term follow-up. The frequency of MGUS is 1% of patients >50 years and 3% of those >70 years. Because of its high prevalence and the multiple fields of clinical practice in which these patients are seen, it is of great importance to know whether the M-protein will remain stable and benign or, on the contrary, progress to a symptomatic disease.

At the Mayo Clinic 241 patients with an apparently benign monoclonal gammopathy were followed for 20 to 35 years (median, 22 years). Abnormal physical findings or laboratory abnormalities such as anemia, thrombocytopenia, or impairment of renal function in some patients were due to unrelated disorders. The median initial M-protein concentration was 17 g/L, and the median percentage of bone marrow plasma cells at diagnosis was 3%. After 20 to 35 years of follow-up, the 241 patients were divided into four groups (Table 1). The actuarial risk of malignant transformation was 17% at 10 years after detection and 33% at 20 years; the disorders consisted of MM (39 cases), primary amyloidosis (8 cases), macroglobulinemia (7 cases), and malignant lymphoproliferative disorders (5 cases). The interval between the recognition of the M-protein and the diagnosis of a serious disease ranged from 2 to 29 years (median, 10 years) (Table 2) (16). No features at diagnosis were useful for distinguishing patients who did not progress from those in whom a malignant change developed. A few (3%) of the patients with monoclonal gammopathy actually had two M-proteins (biclonal gammopathy). The clinical findings are similar to those with monoclonal gammopathy (17). For a review of monoclonal gammopathies for their association with other conditions, see ref. 18.

Multiple Myeloma

MM is characterized by the neoplastic proliferation of a single clone of plasma cells that produce a monoclonal immunoglobulin.

Epidemiology and etiology. The annual incidence of MM is 4:100,000. It represents 1% of all malignant diseases and slightly more than 10% of the hematologic malignancies. The apparent increase in incidence rate during the past several decades is probably related to the increased availability and use of medical facilities and to better diagnostic techniques. Its incidence in African-Americans is twice that in whites. The median age at diagnosis is 62 years, and only 3% of the patients in our referral population are younger than 40 years.

The cause of MM is unknown. Radiation may play a role in some patients. Exposure to herbicides, insecticides, and benzene may be associated with an increased risk, but this is difficult to prove. Its occurrence in two or more first-degree relatives suggests a genetic element, but this is an uncommon event.

Clinical manifestations. Bone pain is present at diagnosis in more than two-thirds of patients. Loss of height is common. Weakness and fatigue are frequent symptoms and are often related to anemia. The initial symptoms may result from renal failure, hypercalcemia, infection, or amyloidosis. The major laboratory features are shown in Table 3.

The diagnosis of MM depends on the presence of ≥10% plasma cells in the bone marrow or histologic proof of a plasma cell plus one of the following: (a) M-protein in serum (usually >30 g/L), (b) M-protein in urine, or (c) lytic bone lesions. The patient must have the usual clinical features of MM and must be differentiated from MGUS, SMM, primary amyloidosis, connective tissue disorders, metastatic carcinoma, lymphoma, leukemia, and chronic infections. An increased plasma

<table>
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<th>Table 1. Course of 241 patients with MGUS.</th>
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<td><strong>Group</strong></td>
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<td>-----------</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
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* Median duration was 22 years.
Source: Kyle RA (16); reprinted by permission of Mayo Fondation.

<table>
<thead>
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<th>Table 2. Results of long-term follow-up of MGUS patients.</th>
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<td><strong>Years to diagnosis</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Macroglobulinemia</td>
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<tr>
<td>Amyloidosis</td>
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<tr>
<td>Lymphoproliferative</td>
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<tr>
<td><strong>Total</strong></td>
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* Actuarial rate: 17% at 10 years and 33% at 20 years.
Table 3. Major laboratory features of MM.

<table>
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<th>Findings</th>
<th>% of MM patients affected</th>
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<tr>
<td>Hemoglobin ≤ 120 g/L</td>
<td>65</td>
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<tr>
<td>Serum calcium ≥ 2.75 mmol/L</td>
<td>14</td>
</tr>
<tr>
<td>Serum creatinine ≥ 153 μmol/L</td>
<td>23</td>
</tr>
<tr>
<td>Serum M-protein present</td>
<td>92</td>
</tr>
<tr>
<td>Urine M-protein present</td>
<td>75</td>
</tr>
<tr>
<td>M-protein in serum or urine (or both)</td>
<td>99</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>75</td>
</tr>
<tr>
<td>Bone marrow plasma cells ≥ 10%</td>
<td>90</td>
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</table>

cell labeling index of the bone marrow and circulating monoclonal plasma cells in the peripheral blood are characteristic of MM. The concentrations of uninvolved immunoglobulins are usually decreased in MM but may also be decreased in MGUS and SMM. SMM is characterized by the presence of an M-protein in the serum ≥ 30 g/L and bone marrow containing ≥ 10% plasma cells but no anemia, hypercalcemia, renal insufficiency, lytic bone lesions, and a stable course during long-term follow-up (19). Measurement of β2-microglobulin, the presence of J chains in plasma cells, an increased concentration of plasma cell acid phosphatase, and reduced numbers of CD4 T lymphocytes are not reliable for differentiating benign from malignant plasma cell proliferative processes.

Prognostic factors. The median duration of survival for patients with MM ranges from 2.5 to 3 years, but there is considerable variability. Prognostic factors include β2-microglobulin, plasma cell labeling index, lactate dehydrogenase, thymidine kinase, C-reactive protein, serum albumin, creatinine, age, plasmablastic morphology, anemia, hypercalcemia, and thrombocytopenia. In our practice, we find that the plasma cell labeling index and β2-microglobulin concentrations are the most significant independent prognostic factors (20).

Variants of MM. Plasma cell leukemia is characterized by the presence of > 20% plasma cells in the peripheral blood and an absolute plasma cell count > 2 × 10⁹/L. This disorder is classified as primary when it presents de novo (60% of cases) and as secondary when it is a leukemic transformation of a previously recognized MM (40%) (21). Patients with primary plasma cell leukemia are younger and have a greater incidence of hepatosplenomegaly and lymphadenopathy, a higher platelet count, fewer bone lesions, a smaller serum M-component, and a longer survival than patients with secondary plasma cell leukemia.

Solitary plasmacytoma of bone is diagnosed on the basis of histologic proof of a plasma cell tumor without evidence of MM. Complete skeletal radiographs must show no other lesions, the bone marrow must contain no evidence of MM, and immunoelectrophoresis or immunofixation of the serum and concentrated urine should show no M-protein. Exceptions to the last criterion occur, but treatment of the solitary lesion usually results in disappearance of the M-protein. Solitary plasmacytomas are usually located in the spine or long bones of the extremities. Therapy consists of radiation in the range of 40 to 50 Gy. There is no evidence that chemotherapy affects the incidence of conversion of a solitary plasmacytoma to MM. Overt MM develops in ~55% of the patients, and new bone lesions or local recurrence develops in ~10% (22). Progression to MM usually occurs within 3 to 4 years (23).

Extradural plasmacytoma is characterized by a plasma cell tumor that arises outside the bone marrow; in ~80% of the cases, it is located in the upper respiratory tract. It may also occur in the gastrointestinal tract, central nervous system, urinary bladder, thyroid, breasts, testes, parotid gland, and lymph nodes. IgA M-protein predominates. The diagnosis depends on the finding of a plasma cell tumor in an extradural location and the absence of MM on bone marrow examination, radiography, and appropriate studies of serum and urine. Treatment consists of tumoricidal radiation. Recurrences occur in ~25% of patients, but development of typical MM is uncommon (24).

Waldenström Macroglobulinemia

This disorder consists of a monoclonal proliferation of plasma cells and B lymphocytes producing an IgM M-protein. In our practice, it is one-seventh as common as MM. The cause is unknown. The median age at diagnosis is 63 years, and there is a slight predominance of the disorder in males.

Clinical manifestations. Weakness, fatigue, bleeding, weight loss, and visual or neurologic disturbances are the most common presenting symptoms. Many clinical manifestations result from the hyperviscosity syndrome, which consists of oronasal bleeding or purpura; visual disturbances such as blurring or loss of vision, retinal hemorrhages, exudates, and venous congestion; neurologic conditions consisting of dizziness, headache, vertigo, hearing loss, ataxia, paresthesias, or somnolence, and cardiovascular disorders characterized by hypervolemia and congestive heart failure.

Physical examination may reveal pallor, hepatosplenomegaly, and lymphadenopathy. Results for hemoglobin and hematocrit are often spuriously low because of the increased plasma volume. A tall, narrow peak or dense band of γ mobility is seen on electrophoresis. The urine contains a monoclonal light chain in 80% of patients. Although the bone marrow aspirate is often hypocellular, the biopsy specimen is hypercellular and extensively infiltrated by lymphocytes, plasma cells, and lymphoplasmacytoid cells.

Differential diagnosis. The diagnosis of macroglobulinemia depends on the presence of typical symptoms, physical findings, the presence of an IgM M-protein in the serum, and a lymphoplasma cell proliferation in the bone marrow. Macroglobulinemia must be differentiated from MM, lymphoma, other lymphoproliferative disorders, chronic lymphocytic leukemia, and MGUS of the IgM type.

Heavy-Chain Diseases

HCDs are lymphoplasma cell proliferative disorders characterized by the production of an M-protein consist-
ing of an incomplete heavy chain devoid of light chains. There are three major types: $\gamma$, $\alpha$, and $\mu$.

$\gamma$-HCD. The $\gamma$ chain is incomplete, with large deletions of amino acids, including the entire $C_{\gamma}1$ domain. The median age at diagnosis is ~60 years, but several patients younger than 20 years have been recognized. Its clinical picture has been described as a lymphomatous illness, but its features are variable (25, 26). The most frequent presenting symptoms are weakness, fatigue, and fever, but edema of the uvula and palate due to Waldayer ring involvement, skin infiltration, and enlargement of the parotid gland or thyroid have been reported. It usually presents as a lymphoproliferative disorder, with hepatosplenomegaly and lymphadenopathy in ~60% of patients. The duration of symptoms before diagnosis has ranged from a few weeks to >20 years. Autoimmune disorders such as rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, Hashimoto thyroiditis, and myasthenia gravis have been noted.

Most cases have normocytic, normochromic anemia. In several instances, a Coombs-positive autoimmune hemolytic anemia has been recognized. All patients have a monoclonal $\gamma$ heavy chain in the serum, but the protein electrophoretic pattern often shows a broad-based $\gamma$ band or hypogammaglobulinemia rather than the expected localized band. The amount of $\gamma$ heavy-chain protein in 24-h urine ranges from undetectable to 20 g; the majority of patients excrete <1 g of protein. Bence Jones proteinuria is not present. The bone marrow and lymph nodes contain an increased number of plasma cells, lymphocytes, and lymphoplasmacytoid cells. The diagnosis depends on the demonstration of a monoclonal $\gamma$ heavy chain in the serum or urine.

The prognosis of $\gamma$-HCD is variable because the clinical course may range from an asymptomatic state to a rapidly progressive disease. The median duration of survival in 49 patients for whom such data were available was 12 months (range 1–264 months) (27).

$\alpha$-HCD. $\alpha$-HCD, the most common type of HCD, is characterized by the presence of a monoclonal $\alpha$ chain with extensive internal deletions encompassing the $V_\alpha$ region and the entire first constant domain. Although most common in the Mediterranean area or the Middle East, it has been seen in all parts of the world. It usually develops in the second or third decade of life but has been reported in both children and the elderly. Poor hygiene and socioeconomic status are important risk factors. About 60% of patients are male. The two major clinical manifestations are (a) gastrointestinal tract involvement, characterized by severe malabsorption with loss of weight, diarrhea, and steatorrhea, and (b) respiratory tract involvement (rare). The gastrointestinal tract is infiltrated with lymphocytes, plasma cells, or immunoblasts, and the condition is indistinguishable from "immunoproliferative small intestinal disease" except for the demonstration of $\alpha$ heavy chains in the cells (28).

The serum protein electrophoretic pattern shows a broad band in the $\alpha_2$ or $\beta$ regions in one-half of patients and is normal in the remainder. The diagnosis depends on the recognition of a monoclonal $\alpha$ heavy chain in the serum, jejunal fluid, lymphocytes, or plasma cells. The amount of $\alpha$ chain in the urine is small, and Bence Jones proteinuria is absent. The bone marrow is normal. The course of $\alpha$-HCD is variable but generally progressive. Spontaneous remissions have occurred, and some patients have responded to a trial of antibiotics. Cyclophosphamide, Adriamycin (doxorubicin), vincristine, and prednisone ("CHOP") or cyclophosphamide, Adriamycin, teniposide, and prednisone ("CHVP") (29) should be given in the event of progressive disease.

$\mu$-HCD. This disease is characterized by a monoclonal $\mu$ heavy chain in which the $V_\mu$ domain is absent; other deletions may also occur. Most patients have a chronic lymphoproliferative process that is often indistinguishable from chronic lymphocytic leukemia or lymphoma. The serum of 40% of patients contains a monoclonal peak. Two-thirds have Bence Jones proteinuria. Increases of lymphocytes, plasma cells, and lymphoplasmacytoid cells in the bone marrow are common. Vacuolization of the plasma cells may be prominent. The diagnosis depends on the demonstration of a $\mu$ heavy chain in the serum. The course of the disease is variable; the duration of survival ranges from <1 month to 11 years (median, 24 months) (30).

Primary Amyloidosis

Primary systemic amyloidosis is characterized by fibrils composed of the variable portion of a monoclonal light chain. The annual incidence is 8.9:1,000,000. The median age is 64 years. Weakness, fatigue, and weight loss are the most frequent symptoms. Paresthesias, light-headedness, syncope, change in voice, macroglossia, dyspnea, pedal edema, and steatorrhea may occur (31).

The liver is palpable in about one-fourth of patients, and splenomegaly is found in only 5%. Macroglossia is present in almost 10% of patients at the time of diagnosis. Purpura is common and often involves the neck and face, particularly the upper eyelids. The skin is fragile and may be easily traumatized during physical examination.

Approximately one-third of patients have a nephrotic syndrome at the time of diagnosis. Congestive heart failure is present at diagnosis in nearly one-fifth of patients, one-eighth present with orthostatic hypotension, and almost one-fifth have peripheral neuropathy. Congestive heart failure or orthostatic hypotension often develops during the course of the disease. The presence of one of these syndromes and an M-protein in the serum or urine raises a strong suspicion of amyloidosis.

Anemia is not a prominent feature of amyloidosis and, when present, is usually due to renal insufficiency, MM, or gastrointestinal bleeding. Thrombocytosis (platelets >500,000 × 10^9/L) occurs in almost 10% of patients and may be an important clue to the diagnosis. Functional hypoplasplenism is one cause of thrombocytosis. Some degree of renal insufficiency occurs in almost half of patients at the time of diagnosis. Serum creatinine is >150 $\mu$mol/L in one-fifth, and alkaline phosphatase is increased in ~25% of patients at diagnosis. Hyperbilirubinemia is an infrequent finding; when present, it is an
ominous sign. Prothrombin time is prolonged in 15% of patients, and thrombin time is increased in ~40%. Factor X is decreased in <5% of patients and is rarely the cause of bleeding. Serum carotene and vitamin B_{12} concentrations are decreased in ~5% of patients.

The serum protein electrophoretic pattern shows a localized band or M-peak in almost one-half of patients; even when present, the peak is usually of modest size and often is not easily recognized in the densitometric tracing. Hypogammaglobulinemia is present in about one-fifth of patients at diagnosis, and the remainder have a normal-appearing pattern. Immunelectrophoresis or immunofixation of the serum reveals an M-protein in two-thirds of patients. Almost one-half have a monoclonal heavy chain in the serum, whereas >20% have only a free monoclonal light chain. Of our patients with an M-protein, ~70% have λ light chains; in contrast, two-thirds of patients with MM have κ light chains.

Immunelectrophoresis and immunofixation of an adequately concentrated urine specimen reveal an M-protein in more than two-thirds of patients. Currently, an M-protein is found at diagnosis in 90% of our patients with amyloidosis. Almost three-fourths of patients have 10% or fewer plasma cells in the bone marrow. Although ~15% of our patients have >20% plasma cells in the bone marrow, they usually do not have symptomatic MM.

The diagnosis depends on the demonstration of amyloid deposits in tissue. Immunohistochemical staining characteristically reveals a reaction of the fibrils with κ or λ antisera. The initial diagnostic procedure should be abdominal fat aspiration because results of this test are positive in ~80% of patients. A bone marrow aspiration and biopsy should be performed and the specimens stained with Congo red because the marrow contains amyloid in more than one-half of amyloidosis patients. If the results of bone marrow and abdominal fat aspirations are negative, a rectal biopsy should be performed. The submucosa must be included because it contains more vessels and produces positive findings in ~75% of patients. If results at these sites are negative, tissue should be obtained from a suspected involved organ such as the kidney, liver, heart, or sural nerve.

**Prognosis.** The current median duration of survival for patients with primary amyloidosis is ~14 months. Survival mainly depends on the associated syndrome. The duration of survival is <6 months from the onset of congestive heart failure, but >2 years in patients presenting with only peripheral neuropathy.