Treatment of the lymphoid neoplasms should follow guidelines of therapy for non-AIDS patients (see Chap. 302). Since these tumors generally follow a more aggressive course in AIDS patients. response rates and duration of responses are less favorable than in a non-AIDS population.

A number of attempts at immune reconstitution have been undertaken. These have included bone marrow transplantation. especially between identical twins when one of the pair has AIDS; infusion of histocompatible lymphocytes; and administration of soluble mediators such as interleukin 2 and interferon gamma. Temporary partial reconstitution of the immune response has been noted in some cases.

There is no cure for AIDS, and no antiretroviral regimen is capable of eliminating HIV completely from infected individuals. As a consequence. the prognosis for infected individuals, particularly those that have advanced to symptomatic disease. is grave. Nonetheless, at least one drug (zidovudine) causes limited prolongation of survival in AIDS patients and a delay in the progression of disease in infected individuals. It is generally felt that the ultimate chemotherapeutic regimen for HIV infection. which it is hoped will lead to it becoming a chronic manageable disease. will be a combination of several antiretroviral agents acting at different phases of the HIV life cycle together with an immunoenhancing agent.

PREVENTION Education. counseling. and behavior modification are the cornerstones of prevention of HIV infection. Widespread voluntary testing for HIV infection together with counseling of infected individuals should prove helpful in behavioral modification programs among infected individuals who would otherwise be unaware of their HIV status and who could potentially infect sexual partners. In addition, infected individuals may benefit from early therapeutic intervention even if they are asymptomatic. The incidence of new infections per year among homosexual and bisexual men in certain high-prevalence cities such as San Francisco has decreased dramatically from the early years of the epidemic. This has resulted, at least in part. from behavioral modifications regarding the number of sex partners and safe sexual practices. Several studies indicate that condom use decreases the risk of HIV transmission.

Screening of the blood supply for antibodies to HIV has almost eliminated infections among transfusion recipients and hemophiliacs who require replacement of plasma components. Continuing high rates of new infections among intravenous drug users. their heterosexual partners, and children born to intravenous drug users or to the female sexual partners of intravenous drug users will require intensive efforts aimed at treatment of drug abuse together with behavioral modification.

Health care workers should practice universal precautions when handling blood and body fluids and follow all guidelines for the prevention of transmission of HIV and hepatitis B virus that have been issued by the Centers for Disease Control (see Chap. 83).

The development of a vaccine to prevent infection and/or disease with HIV will be an important tool in the strategy for world-wide containment of the AIDS epidemic. Several candidate vaccines are undergoing early phase I testing in humans. In the'monkey model of simian immunodeficiency virus (SIV). immunization with whole killed SIV is effective in protecting animals from challenge with live virus by preventing either infection or the development of disease following infection. These studies lend optimism to the feasibility of developing a safe and effective vaccine for HIV in the future.

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265 PLASMA CELL DISORDERS

DAN L. LONGO

GENERAL PRINCIPLES The plasma cell disorders are monoclonal neoplasms related to each other by virtue of their development from common progenitors in the B-lymphocyte lineage. Multiple myeloma, Waldenstrom's macroglobulinemia. primary amyloidosis (see Chap. 266). and the heavy chain diseases comprise this group and may be designated by a variety of synonyms such as monoclonal gammopathies. paraproteinemias, plasma cell dyscrasias. and dysproteinemias. A schema for the normal development of B lymphocytes is depicted in Fig. 265-1. Mature B lymphocytes destined to produce IgG, bear surface immunoglobulin molecules of both M and G heavy chain isotypes with both isotypes having identical idiotypes (variable regions). Under normal circumstances. maturation to antibody-secreting plasma cells is stimulated by exposure to the antigen for which the surface immunoglobulin is specific: however, in the plasma cell disorders the control over this process is lost. The clinical manifestations of all the plasma cell disorders relate to the expansion of the neoplastic cells. to the secretion of cell products (immunoglobulin molecules or subunits. lymphokines), and to some extent to the host's response to the tumor.

There are three categories of structural variation among immunoglobulin molecules that form antigenic determinants. and these are used to classify immunoglobulins (Chap. 13). *Isotypes* are those determinants that distinguish among the main classes of antibodies of a given species and are the same in all normal individuals of that species. Therefore. isotypic determinants are by definition recognized by antibodies from a distinct species (heterologous sera) but not by antibodies from the same species (homologous sera). There are five heavy chain isotypes (M, G. A. D. E) and two light chain isotypes (kappa. lambda). Allotypes are distinct determinants that reflect regular small differences between individuals of the same species in the amino acid sequences of otherwise similar immunoglobulins. These differences are determined by allelic genes. and by definition they are detected by antibodies made in the same species. *Idiotypes* are the third category of antigenic determinants. They are unique to the molecules produced by a given clone of antibody-producing cells. Idiotypes are formed by the unique structure of the antigen binding portion of the molecule.

Antibody molecules (see Fig. 265-2) are composed of two heavy chains (mol wt ~ 50,000) and two light chains (mol wt ~ 25,000). Each chain has a constant portion (limited amino acid sequence variability) and a variable region (extensive sequence variability).

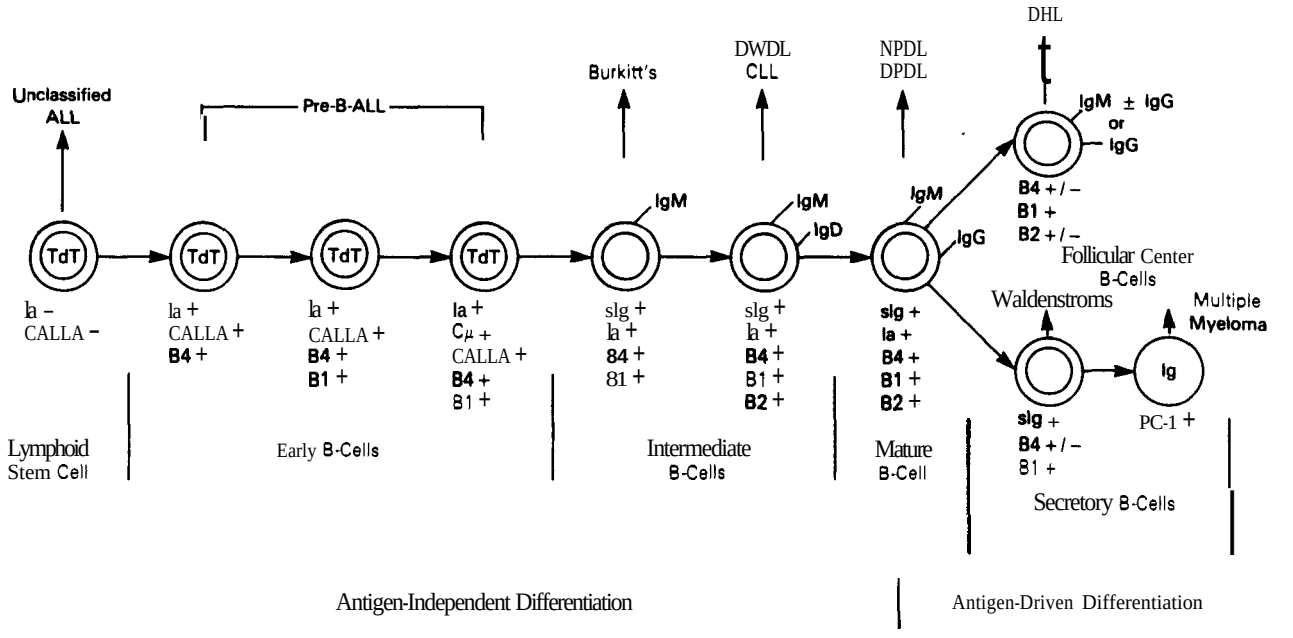
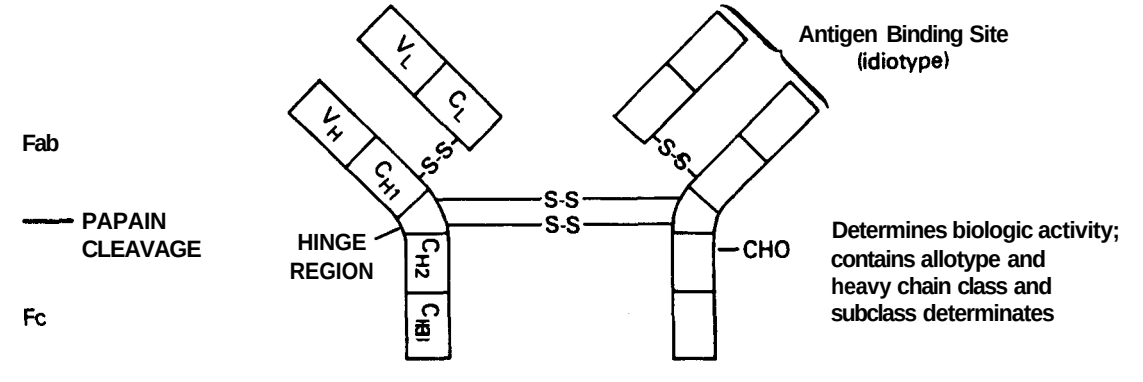


FIGURE 265-1 Schematic representation of the pathway of differentiation of normal B cells. **CALLA, B1, B2, B4.** Ia. PC-1, and slg (surface immunoglobulin) are cell markers used to distinguish discrete stages of development. Terminal transferase (TdT) is a cellular enzyme. The stage of differentiation arrest for each lymphoproliferative disorder is shown. The following abbreviationsare used: **ALL.** acute lymphoblastic leukemia: **DWDL.** diffuse well-differentiated lymphocytic lymphoma: **CLL.** chronic lymphocytic leukemia: **NPDL, nodular** poorly differentiated lymphocytic lymphoma: **DPDL,** diffuse poorly differentiated lymphocytic lymphoma; **DHL,** diffuse histiocytic or large-cell lymphoma.

The light and heavy chains arc linked by disulfide bonds and arc aligned **so** thcir variablc regions arc adjacent to one anothcr. This variable rcgion forms the antigen recognition site of the antibody molccculc; its uniquc structural features form a particular set of determinants called idiotypes that arc reliable markers for a particular clonc of cclls bccausc cach antibody is formed and sccrctcd by a single clonc. Each chain is specified by distinct gcncs. synthcsizcd separately, and asscmblcd into an intact antibody molccculc after translation (see Fig. **265-3).** Bccausc of the mechanics of the gcnc rearrangements ncccssary to specify the immunoglobulin variable regions (VDJ joining for the heavy chain. VJ joining for the light chain; see Fig. **265-3),** a particular clone rearranges only one of the two chromosomes **to** produce an immunoglobulin molccculc of only one light chain isotypc and only one allotype (allelic exclusion). After exposure to antigen. the variable rcgion may bccomc associatcd with a new heavy chain isotypc (class switch). Each clonc of cclls performs thcsc scqucntial gene arrangements in a uniquc way. This rcsults in cach clone producing a uniquc immunoglobulin molccculc. In most cclls, light chains are synthcsizcd in slight cxccss. arc sccrctcd as free light chains by plasma cells. and arc clcarcd by the kidncy. but less than 10 mg of such light chains is excrctcd per day.

Electrophoretic analysis of components of the scrum proteins permits determination of the amount of immunoglobulin in the scrum (Fig. **265-4).** The variety **of** immunoglobulins move hctcrogcncously in an electric field and form a broad peak in the gamma rcgion. The gamma globulin region of the clectrophorctic pattern is usually increased in the serum of patients and animals with plasma ccll tumors. There is a sharp spike in this rcgion called an **M** componcnt

FIGURE 265-2 Schematic depiction of an IgG molecule. Each molecule consists of two heavy and two light chains linked by disulfide bonds. There are two types of light chains, kappa (genes on chromosome 2) and lambda (chromosome 22). each containing two domains. There are 10 types of heavy chains: **4** types of G (G1 to G4), 2 of **A** (A1, A2), **2** of **M** (**M1, M2**), and 1 each of **D** and **E** (all on chromosome 14). each with four domains. **A** domain is 100 to 110 amino acids in length. Within each domain is an intrachain disulfide bond that produces a loop. V_H (variable domain of the heavy chain) and V_L (variable domain of the light chain) form an antigen binding site whose unique determinants form an idiotype. Immunoglobulins of the same isotype (e.g., IgG1κ) differ between individuals. The determinants that distinguish them are called allotypic determinants and are located on C_L (constant domain of the light chain) and C_{H2} (second constant domain of the heavy chain). C_{H2} is also the main site of glycosylation (CHO) and complement binding. Papain cleaves the molecule into antigen-binding (Fab) and crystallizable (Fc) components. The portion of the heavy chain in an Fab fragment is called the Fd piece. Fc receptors on cells bind to the C_{H3} domain. IgM and IgA occur as polymers and each unit of two heavy and two light chains is connected by a J (joining) chain. The heavy chain isotypes determine the function of the antibody.



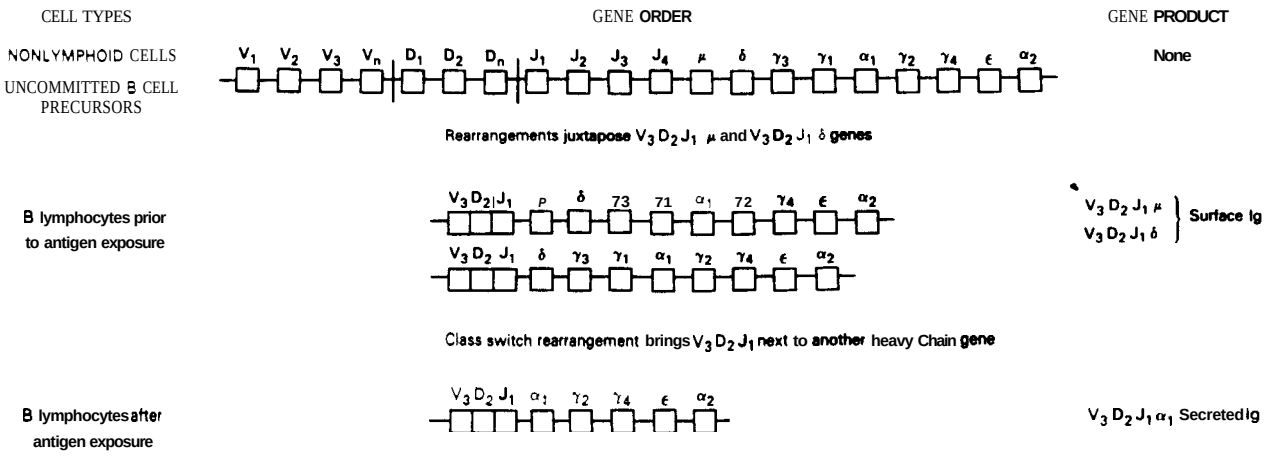
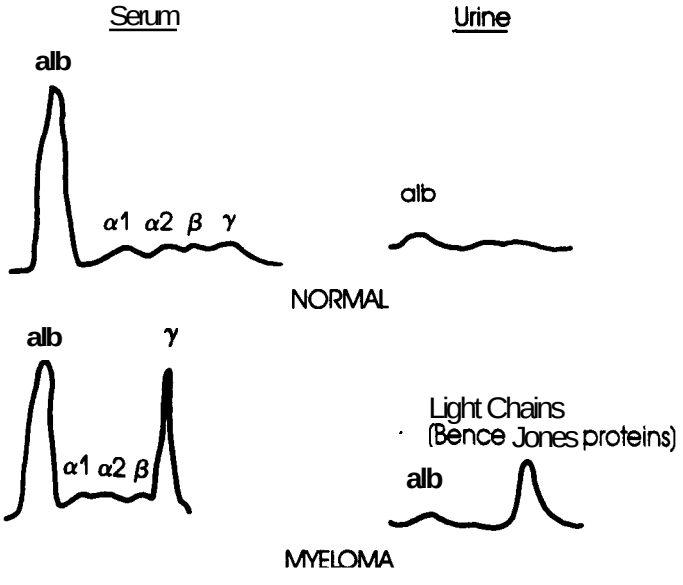


FIGURE 265-3 Schematic diagram of the organization and translocation of immunoglobulin genes. Immunoglobulin heavy chains are encoded by four distinct genetic elements. variable (Igh-V), diversity (Igh-D), joining (Igh-J), and constant (Igh-C) genes. The variable region of the immunoglobulin heavy chain is encoded by the V. D. and J genes. The same variable region may be associated with any of the 10 heavy chain constant region genes. In the germline genome (all cells except B cells) the V, D, and J genes are widely separated and there are numerous forms of each. Once a cell becomes committed to B-cell differentiation, a single V gene and a single D gene translocate to a single J gene. and the intervening genetic material is excised. This is called VDJ joining. The newly formed VDJ gene is transcribed into a single message along with either an M or D isotype C gene. Upon exposure to antigen. another rearrangement may occur so that the VDJ gene may be associated with a G, A or E isotype C gene. In light chain genes. there appear to be no D genes. and thus. light chain variable regions are formed by VJ joining.

(M for monoclonal). Less commonly the M component may appear in the beta, or alpha, globulin region. The antibody must be present at a concentration of at least 5g/L (0.5g/dL) to be detectable by this method. This corresponds to approximately 10^9 cells producing the antibody. Contirmation that such an M component is truly monoclonal relies on the use of immunoelectrophoresis that shows a single light and heavy chain type. Hence, immunoelectrophoresis and electrophorcsis provide qualitative and quantitative assessment of the M component. respectively. Once the presence of an M Component has been confirmed, clcctrophoresis provides the more practical information for managing patients with monoclonal gammopathies. In a given patient, the amount of M component in the serum is a reliable measure of the tumor burden. This makes the M component an excellent tumor marker; yet it is not specific enough to be used to screen asymptomatic patients. In addition to the plasma cell disorders. M components may be detected in other lymphoid neoplasms such as chronic lymphocytic leukemia and lymphomas of B- or T-cell origin; nonlymphoid neoplasms such as chronic myelogenous leukemia, breast and colon cancer; a variety of nonneoplastic conditions such as cirrhosis, sarcoidosis, parasitic diseases, Gaucher's disease. and pyoderma gangrenosum; and a number of autoimmune conditions. including rheumatoid arthritis. myasthenia gravis. and cold agglutinin disease. A very rare skin disease known as lichen myxcdcmatosus or papular mucinosis is associated with a monoclonal gammopathy. Highly cationic IgGλ is deposited in the dermis of patients with this disease. It is unclear whether this organ specificity reflects the specificity of the antibody for some antigenic Component of the dermis. The nature of the M component is variable. It may be an intact antibody molecule of any heavy chain subclass, or it may be an altered antibody or fragment. Isolated light or heavy chains may be produced. In some plasma cell tumors such as extramedullary or solitary bone plasmacytomas. less than a third of patients will have an M component. In about 20 percent of myelomas, only light chains are produced and in most cases are secreted in the urine as Bence Jones proteins. The frequency of myelomas of a particular heavy chain class is roughly proportional to the serum concentration. so that IgG myelomas are more common than IgA and IgD myelomas. In some cases, the antigen specificity of the monoclonal antibody is known.

FIGURE 265-4 Representative electrophoretic patterns of serum and urine. The upper panel illustrates the normal pattern of serum and urine protein on electrophoresis. Since there are many different immunoglobulins in the serum, their differing mobilities in an electric field produce a broad peak. The lower panel illustrates the patterns of serum and urine proteins in a patient with myeloma. The predominance of a product of a single cell is reflected by a "church spire" sharp peak. The presence of free light chains in the urine is reflected in a peak. as well.



MULTIPLE MYELOMA Definition Multiple myeloma represents a malignant proliferation of plasma cells. The terms multiple myeloma and myeloma may be used interchangeably. The disease results from the uncontrolled proliferation of plasma cells derived from a single clone. The tumor. its products, and the host response to it result in a number of organ dysfunctions and symptoms of bone pain or fracture, renal failure, susceptibility to infection, anemia. hypercalcemia. and occasionally clotting abnormalities. neurologic symptoms. and vascular manifestations of hyperviscosity.

Etiology The etiology of myeloma is not known. Myeloma was found to occur with increased frequency in those exposed to the radiation of nuclear warheads in World War II after a 20-year latency. Although there is no direct evidence implicating oncogenes in human myeloma. the observations of c-*myc* and b-*lym* oncogenes in Burkitt's lymphoma. the high incidence of chromosomal translocations in

human B-cell tumors. and the role of type C RNA viruses in murine plasmacytoma formation suggest that cells of the B-cell lineage may be susceptible to growth deregulation by such stimuli. The murine plasmacytoma models are particularly interesting in that there is evidence that the induction of plasmacytomas may require exposure to foreign antigens as well as a cellular event. This suggests that chronic antigenic stimulation may play a role in the transformation of a particular B-cell clone. There is also some evidence for a genetic predisposition to myeloma in humans. Patients with myeloma have a significantly higher incidence of expressing the Glm(x) heavy chain allotype marker, and there is a weak but significant linkage disequilibrium that shows the HLA-B5 determinant being expressed more commonly than expected in myeloma patients. There is the possibility that the neoplastic event in myeloma may involve cells earlier in B-cell differentiation than the plasma cell. Circulating B cells bearing surface immunoglobulin that share the idiotype of the M component are present in myeloma patients. It is possible that the malignant clone escapes normal control mechanisms at a pre-plasma cell stage of differentiation and the chronic exposure to a particular antigenic stimulus drives the cell to terminal differentiation. It remains difficult to distinguish benign from malignant plasma cells on the basis of morphologic criteria in all but a few cases.

Incidence and prevalence Myeloma is primarily a disease of the elderly and increases in incidence with age. The median age at diagnosis is 64 years. The disease is rare under age 40. The yearly incidence is around 3 per 100,000 and remarkably similar in a variety of countries throughout the world. Males are slightly more commonly affected than females and blacks have nearly twice the incidence of whites. In the age group over 25 years of age the incidence is 30 per 100,000.

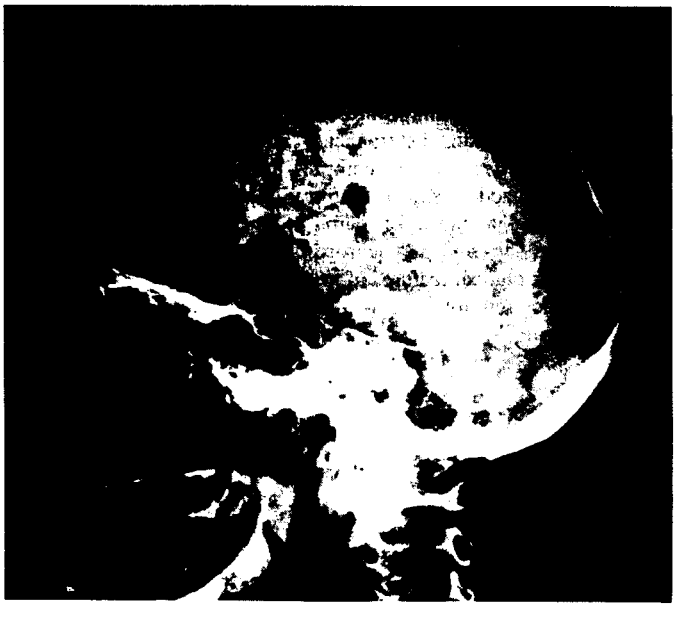
Pathogenesis and cllnlcai manifestations (Table 265-1) Bone pain is the most common symptom in myeloma and is present in nearly 70 percent of patients. The pain usually involves the back and ribs. and unlike the pain of metastatic carcinoma which often is worse at night. the pain of myeloma is precipitated by movement. Persistent localized pain in a patient with myeloma usually signifies a pathologic fracture. The bone lesions of myeloma are caused by the proliferation of the tumor cells and the activation of osteoclasts which destroy the bone. The osteoclasts respond to osteoclast activating factors (OAF) made by the myeloma cells (OAF activity can be mediated by several cytokines including interleukin I, lymphotoxin. and tumor necrosis factor). However, production of these factors stops following administration of corticosteroids or interferon-gamma. The bone lesions are lytic in nature and are rarely associated with osteoblastic new bone formation; therefore, radioisotopic bone scanning is less useful in diagnosis than plain radiography. The bony lysis results in substantial mobilization of calcium from bone, and serious acute and chronic complications of hypercalcemia may dominate the clinical picture (see below). Localized bone lesions may expand to the point that mass lesions may be palpated, especially on the skull (Fig. 265-5), clavicles, and sternum, and the collapse of vertebrae may lead to symptoms of spinal cord compression.

The next most common clinical problem in patients with myeloma is susceptibility to bacterial infections. The most common infections are pneumonias and pyelonephritis. and the most frequent pathogens are *Streptococcus pneurnoniae. Staphylococcus aureus*, and *Klebsiella pneumoniae* in the lungs and *Escherichia coli* and other gram-negative organisms in the urinary tract (Chap. 82). In about 25 percent of patients recurrent infections are the presenting features, and over 75 percent of patients will have a serious infection at some time in their course. The susceptibility to infection has several contributing causes. First. patients with myeloma have diffuse hypogammaglobulinemia if the M component is excluded. The hypogammaglobulinemia is related to both decreased production and increased destruction of normal antibodies. Moreover. some patients generate a population of circulating regulatory cells in response to their myeloma that can suppress normal antibody synthesis. In the case of IgG mycloma. normal IgG antibodies are broken down more rapidly than normal because the catabolic rate for IgG antibodies varies directly with the serum concentration. The large M component results in fractional catabolic rates of 8 to 16 percent instead of the normal 2 percent. These patients have very poor antibody responses. espccialiy to polysaccharide antigens such as those on bacterial cell walls. Such responses are normally T-cell-independent. Most measures of T-cell function in myeloma arc normal but a subset of CD4+ cells may be decreased. Granulocyte lysozyme content is low and granulocyte migration is not as rapid as normal in patients with myeloma. probably

TABLE 265-1 Pathogenesis and clinical manifestations of multiple myeloma

Clinical linding	Underlying cause	Pathogenic mechanism
Hypercalcemia. pathologic fractures. cord compression, lytic bone lesions. osteoporosis. bone pain	Skeletal destruction	Tumor expansion: production of osteoclast activating factors (OAF) by tumor cells
Renal failure	Light chain proteinuna, hypercalcemia. urate nephropathy. amyloid glomerulopathy (rare)	Toxic effects of tumor products: light chains. OAF. DNA breakdown products:
	Pyelonephritis	Hypogammaglobulinemia
Anemia	Myelophthisis. decreased production. increased destruction	Tumor expansion: production of inhibitory factors and autoantibodies by tumor cells
Infection	Hypogammaglobulinemia. decreased neutrophil migration	Decreased production due to tumor-induced suppression: increased IgG catabolism
Neurologic symptoms	Hyperviscosity. cryoglobulins. amyloid deposits	Products of tumor: properties of M component: light chains
	Hypercalcemia. cord compression	OAF
Bleeding	Interference with clotting factors. amyloid damage of endothelium. platelet dysfunction	Products of tumor; antibodies to clotting factors: light chains; antibody coating of platelets
Mass lesions		Tumor expansion

FIGURE 265-5 Bony lesions in multiple myeloma. The skull demonstrates the typical "punched out" lesions characteristic of multiple myeloma. The lesion represents a purely osteolytic lesion with little or noosteoblastic activity. *(Courtesy of Dr. Geraldine Schechter.)*



the result of a product of the tumor. There are also a variety of abnormalities in complement functions in myeloma patients. All of these factors contribute to the immune deficiency of these patients.

Renal failure occurs in nearly 25 percent of myeloma patients. and some renal pathology is noted in over half. There are many contributing factors. Hypercalcemia is the most common cause of renal failure'. Glomerular deposits of amyloid, hyperuricemia. recurrent infections, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction. However, tubular damage associated with the excretion of light chains is almost always present. Normally. light chains are filtered, reabsorbed in the tubules and catabolized. With the increase in amount of light chains presented to the tubule. the tubular cells become overloaded with these proteins. and tubular damage results either directly from light chain toxic effects or indirectly from the release of intracellular lysosomal enzymes. The earliest manifestation of this tubular damage is the adult Fanconi syndrome (a type 2 proximal renal tubular acidosis) with increased loss of glucose. amino acids, and defects in the ability of the kidney to acidify and concentrate the urine. The proteinuria is not accompanied by hypertension, and the protein is nearly all light chains. Generally, there is very little albumin in the urine because glomerular function is usually normal. When the glomeruli are involved, the proteinuria is nonselective. Patients with myeloma also have a decreased anion gap [i.e., sodium minus (chloride plus bicarbonate)] because the M component is cationic, resulting in retention of chloride. This is often accompanied by hyponatremia that is felt to be artificial (pseudohyponatremia) because each volume of serum has less water as a result of the increased protein.

Anemia occurs in about 80 percent of myeloma patients. It is usually normocytic and normochromic and related both to the replacement of normal marrow by expanding tumor cells and to the inhibition of hematopoiesis by factors made by the tumor. In addition, mild hemolysis may Contribute to the anemia. A larger than expected fraction of paticnts may havc megaloblastic ancmia due to either folate or vitamin B_{12} deficiency. Granulocytopenia and thrombocytopenia are very rare. Clotting abnormalities may be seen due to the failure of antibody-coated platelets to function properly or to the interaction of the M componcnt with clotting factors I, II, V. VII, or VIII. Raynaud's phcnomcnon and impaired circulation may rcsult if the M componcnt forms cryoglobulins. and hypcrviscosity syndromes may dcvclop depending on the physical properties of the M Component (most common with IgM, IgG3, and IgA paraprotcins). Hyperviscosity is defined on the basis of the relative viscosity of Serum as compared to water. Normal relative Serum viscosity is 1.8 (i.e., serum is normally almost twice as viscous as water). Symptoms of hyperviscosity occur at a level of 5 to 6. a level usually reached at paraprotein concentrations of around 40 g/L (4 g/dL) for IgM, 50 g/L (5 g/dL) for IgG3, and 70 g/L (7 g/dL) for IgA.

Although neurologic symptoms occur in a minority of patients. they may have many causes. Hypercalcemia may produce lethargy. weakness, depression, and confusion. Hyperviscosity may lead to headache, fatigue, visual disturbances. and retinopathy. Bony damage and collapse may lead to cord compression, radicular pain, and loss of bowel and bladder control. Infiltration of peripheral nerves by amyloid can be a cause of carpal tunnel syndrome and other sensorimotor mono- and polyneuropathies.

Many of the clinical features of myeloma. e.g., cord compression, pathologic fractures. hyperviscosity. sepsis. and hypercalcemia, can present as medical emergencies. Despite the widespread distribution of Plasma cells in the body. tumor expansion is dominantly within bone and bone marrow and, for reasons unknown, rarely causes enlargement of spleen, lymph nodes, or gut-associated lymphatic tissue.

Diagnosis and staging The classic triad of myeloma is marrow plasmacytosis (>10 percent). lytic bone lesions. and a serum and/or urine M component. The diagnosis may be made in the absence of bone lesions if the plasmacytosis is associated with a progressive increase in the M component over time or if extramedullary mass lesions develop. There arc two important variants of myeloma, solitary bone plasmacytoma and extramedullary plasmacytoma. These lesions are associated with an M component in less than 30 percent of the cases, they may affect younger individuals. and both are associated with median survivals of 10 or more years. Solitary bone plasmacytoma is a single lytic bone lesion without marrow plasmacytosis. Extramedullary plasmacytomas usually involve the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis. Both tumors are highly responsive to local radiation therapy. If an M component is present, it should disappear after treatment. Solitary bone plasmacytomas may recur in othcr bony sites or evolve into myeloma. Extramedullary plasmacytomas rarely recur or progress.

The most difficult differential diagnosis in paticnts with myeloma involves their separation from people with benign monoclonal gammopathies or monoclonal gammopathies of uncertain significance (MGUS). MGUS is vastly more common than myeloma. occurring in 1 percent of the population over age 50 and in up to 10 pcrccnt over age 75. Patients with MGUS usually havc fewer than 20 g/L (2 g/dL) of M components. no urinary Bence Jones protein. lcss than 5 percent marrow plasmacytosis, and no anemia, renal failure. lytic bone lesions, or hypercalcemia. When bone marrow cells are exposed to radioactive thymidine in order to quantitate dividing cells, paticnts with MGUS always have a labcling index lcss than 1 pcrccnt and patients with myeloma always havc a labcling index greater than 1 perccnt. Other discriminators include plasma ccll acid phosphatase and β-glucuronidasc, both of which arc low in MGUS paticnts. and the salmon calcitonin stimulation test, which is positivc only in patients with activc ongoing bonc destruction. Only about 11 pcrccnt of patients with MGUS go on to dcvclop mycloma. Typically. paticnts with MGUS require no therapy.

The clinical evaluation of paticnts with mycloma includes a carcful physical examination searching for tender bones and masses. It is paradoxic that only a small minority of paticnts havc an enlargement of the spleen and lymph nodes, the physiologic sites of antibody production. Chest and bonc radiographs may rcvcal lytic Icsions or diffusc osteopcnia. A complctc blood count with differential may reveal anemia. Erythrocytc scdimcntation ratc is elevated. Very rare patients (—2 pcrccnt) may havc plasma ccll leukemia with more than 2000 plasma cells per microliter. This may be seen in disproportionate frequency in IgD (~12 pcrccnt) and IgE (~25 pcrccnt) myelomas. Serum calcium. urea nitrogen, creatinine. and uric acid may be elevated. Protein electrophoresis and measurcmcnt of scrum immunoglobulins are useful for detecting and characterizing M spikes. supplemented by immunoelcctrophorcsis. which is especially sensitive for identifying low concentrations of M Components not detectable by protein electrophoresis. A 24-h urine specimen is ncccssary to quantitate protein excretion and a concentrated aliquot is used for electrophoresis and immunological typing of any M component. Serum alkaline phosphatase is usually normal even with extensive bone involvement because of the absence of osteoblastic activity. It is also important to quantitate serum beta, microglobulin (see below).

The serum M component will be IgG in 53 percent of patients. IgA in 25 percent. IgD in 1 percent, and 20 percent of patients will have only light chains in serum and urine. Dipsticks for detecting proteinuria are not reliable at identifying light chains. and the heat test for detecting Bence Jones protein is falsely negative in about 50 percent of patients with light chain myeloma. Fewer than 1 percent of patients have no identifiable M component. and these are usually light chain myelomas in which renal catabolism has made them undetectable in the urine. About two-thirds of patients with serum M components also have urinary light chains. The light chain isotype may have an impact on survival. Patients secreting lambda light chains have a significantly shorter overall survival than those secreting kappa light chains. It is not clear whether this is due to some genetically important determinant of cell proliferation or because lambda light chains are more likely to cause renal damage and form amyloid than are kappa light chains. The heavy chain isotype may

have an impact on patient management as well. About half of patients with IgM paraproteins develop hyperviscosity compared to only 2 to 4 percent of patients with IgA and IgG M components. Among IgG myelomas, it is the IgG3 subclass that has the highest tendency to form both concentration- and temperature-dependent aggregates, leading to hyperviscosity and cold agglutination at lower serum concentrations.

The staging system for patients with myeloma is a functional system for predicting survival and is based on a variety of clinical and laboratory tests, unlike the anatomic staging systems for solid tumors. Details of the staging system are given in Table **265-2.** Based upon the hemoglobin, calcium, M component, and degree of skeletal involvement, the total-body tumor burden is estimated to be low (stage I, $<0.6 \times 10^{12}$ cells per square meter), intermediate (stage II, 0.6 to 1.2×10^{12} cells per square meter), or high (stage III, $>1.2 \times 10^{12}$ cells per square meter). and the stages are further subdivided on the basis of renal function (A if serum creatinine <2 mg/dL, B if >2). Patients in stage IA have a median survival of more than 5 years and those in stage IIIB about 15 months. Beta, microglobulin is a protein of 11,000 mol wt with homologies with the constant region of immunoglobulins that is the light chain of the class I major histocompatibility antigens (HLA-A, -B. -C) on the surface of every cell. Serum beta, microglobulin is the single most powerful predictor of survival and can substitute for staging. Paticnts with beta, microglobulin levels less than 0.004 g/L have a median survival of 43 months and those with levels highcr than 0.004 g/L only 12 months. It is also felt that once the diagnosis of mycloma is firm. histologic fcaturcs of atypia may also cxcrt an influence on prognosis.

Treatment and course About 10 pcrccnt of paticnts with myeloma will havc an indolent courscdemonstrating only very slow progression of discasc over many years. Such paticnts only rcquirc antitumor therapy when the scrum mycloma protein rises above 50 g/L (5 g/dL) or progressive bonc lesions dcvclop. Paticnts with solitary bonc plasmacytomas and cxtramcdullary plasmacytomas may be expected to enjoy prolonged, disease-free survival after local radiation therapy to a dose of around 40 **Gy.** There is a low incidence of occult marrow involvement in patients with solitary bone plasmacytoma. Such patients are usually detected because their serum M component falls slowly or disappears initially only to return after a few months. These patients respond well to systemic chemotherapy.

The vast majority of patients with myeloma require therapeutic intervention. In general. such therapy is of two sorts: systemic chemotherapy to control the progression of myeloma and symptomatic supportive care to prevent serious morbidity from the complications of the disease. All patients with stage II or III disease and stage I patients exhibiting Bence Jones proteinuria, progressive lytic bone lesions, vertebral compression fractures, recurrent infections. or rising serum M component should be treated with systemic combination chemotherapy. Although there are no reported cases of long-term disease-free survival (i.e., cured patients), there is no doubt that therapy can prolong and improve the quality of life for mycloma patients.

The standard treatment has consisted of intermittent pulses of an alkylating agent [L-phenylalanine mustard (L-PAM, melphalan). cyclophosphamide. or chlorambucil] and prcdnisonc administcrcd for 4 to 7 days cvcry 4 to 6 weeks. The alkylating agcnts appear to be roughly equally activc. but resistance to onc agcnt is oftcn accompanied by resistance to the others. The usual doses arc as follows: melphalan, 8 **mg/m²** body surface area per day: cyclophosphamide. 200 **mg/m²** per day: chlorambucil, 8 mg/m² per day: prcdnisonc. 25 to 60 **mg/m²** per day. Bccausc of their near cquivalcncc in antitumor efficacy, **wc** favor cyclophosphamide as the alkylating agcnt bccause it is **lcss** toxic to the marrow stem ccll compartment and rcsults in a lower incidcncc of acute myclodysplastic syndromes than do the othcr alkylating agents. Doses may need adjustment bascd on marrow tolcrancc. Howcvcr, thcrc arc few constraints on the dose of the stcroid pulse and it appcars that morc is bcttcr. Rcccnt cvidcncc suggests that higher dose-intensity of the steroid (i.e., mg/m² per wcck) is associated with significantly longer survival. Paticnts responding to thcrapy gcncrally havc a prompt and gratifying reduction in bonc pain. hypcrcalccmia. and ancmia. and oftcn havc fcwcr infections. The scrum M componcnt lags substantially behind the symptomatic improvcmcnt. oftcn taking 4 to 6 weeks to fall. This fall dcpcnds upon the ratc of tumor kill and the fractional catabolic ratc of immunoglobulin. which in turn dcpcnds **upon** the scrum concentration (for IgG). Light chain cxcrction. with a functional half-life of approximately 6 h. may fall within the first wcck of trcatmcnt. Howcvcr, since urine light chain lcvcls may rclatc to renal tubular function. they arc not a rcliablc mcasurc of tumor cell kill. Calculations of tumor ccll kill arc made by extrapolation of the scrum M-component level and rely heavily on the assumption that cvcry tumor ccll produces immunoglobulin at a constant ratc. The data on which this assumption is based arc rcasonablc, but rcccntly it has been possible to alter the rate of immunoglobulin production of a mycloma in vitro with calcium channel blockers. a linding that may havc clinical utility, for cxamplc. in patients with hypcrviscosity. Thus. it is possible that a treatment might affect immunoglobulin production without killing the tumor ccll. a situation that would rcsult in an overestimation of the antitumor cffccts of the treatment if current criteria for response were applied. About **60** percent of patients will achieve at least a 75 perccnt rcduction in serum M-component lcvcl and tumor cell mass in response to an alkylating agcnt and prcdnisonc. Although this is a tumor reduction of lcss than one log, clinical responses may last many months. Efforts to improve the fraction of patients responding and the degree of response havc involved adding other active chemotherapeutic agents to the trcatmcnt program. Patients with more advanced disease may benefit most from such an approach, but 3- to 5-drug therapy is experimental at this time.

The ideal duration of therapy has not been determined. Most physicians treat every 4 to 6 weeks for I or 2 years. Cessation of therapy is followed by relapse, usually within a year. Rctreatmcnt may be associated with a second responsc in up to 80 perccnt of

TABLE 265-2 Myeloma staging system

Stage	Criteria	Estimated tumor hurdcn ($\times 10^{12}$ cells/m²)
I	All of the following: *1* Hemoglobin >100 g/L (10 g/dL) 2 Serum calcium <12 mg/dL *3* Normal bonc x-ray or solitary lesion *4* Low M-component production *a* IgG level <50 g/L (<5 g/dL) *b* IgA level <30 g/L (<3 g/dL) *c* Urine light chain <4 g/24 h	<0.6 (low)
II	Fitting neither I nor III	0.6–1.20 (intermediate)
III	One or more of the following: *1* Hemoglobin <85 g/L (<8.5 g/dL) *2* Serum calcium (>12 mg/dL) 3 Advanced lytic bone lesions *4* High M-component production *a* IgG level >70 g/L (>7 g/dL) *b* IgA level >50 g/L (>5 g/dL) c Urine light chains >12 g/24 h	>1.20 (high)

SUBCLASSIFICATION BASED ON SERUM CREATININE LEVELS

Level	Stage	Median survival. months
A <2 mg/dL	IA	61
B >2 mg/dL	IIA,B	55
	IIIA	30
	IIIB	15

ALTERNATIVE STAGING BASED ON SERUM BETA, MICROGLOBULIN LEVELS

Level	Stage	Median survival. months
<4 μg/mL	I	43
>4 μg/mL	II	12

patients. Maintenance therapy may prolong the duration of response, but no study has demonstrated this to result in prolonged survival. The regrowth rate of the tumor during relapse accelerates with each relapse. Patients primarily resistant to initial therapy have a median survival of less than a year. High-dose pulsed steroids used alone (200 mg prednisone every other day or 1 g/m² per day methylprednisolone for 5 days) or VAD combination chemotherapy (vincristine, 0.4 mg per day 4-day continuous infusion; doxorubicin, 9 mg/m² per day in a 4-day continuous infusion; dexamethasone, 40 mg per day for 4 days per week for 3 weeks) may offer useful palliation in patients resistant to primary therapy.

About 15 percent of patients die within the first 3 months after diagnosis, and subsequently the death rate is about 15 percent per year. The disease usually follows a chronic course for 2 to 5 years before developing an acute terminal phase usually marked by the development of pancytopenia with a cellular marrow that is refractory to treatment. Widespread organ infiltration by myeloma cells occurs and survival is less than 6 months. About 46 percent of patients die in the chronic phase of disease from progressive myeloma (16 percent) and renal failure (10 percent). sepsis (14 percent), or both (6 percent). Death in the acute terminal phase (26 percent) is chiefly from progressive myeloma (13 percent) and sepsis (9 percent). Five percent of patients die of acute leukemia. myeloblastic or monocytic, and although it has been debated that this is related to the primary disease, it appears more likely to be the result of chronic therapy with alkylating agents. Nearly 23 percent of patients die of myocardial infarction, chronic lung disease, diabetes, or strokes, all intercurrent illnesses related more to the age of the patient group than the tumor.

Supportive care directed at the anticipated complications of the disease may be as important as primary antitumor therapy. The hypercalcemia generally responds well to corticosteroid therapy, hydration. and natriuresis. Calcitonin may add to the inhibitory effects of steroids on bone resorption. Dichloromethane diphosphonate has also been shown to reduce osteoclastic bone resorption. Treatments aimed at strengthening the skeleton, like fluorides, calcium. and vitamin D with or without androgens. have been suggested but are not of proven efficacy. Iatrogenic worsening of renal function may be prevented by the use of allopurinol during chemotherapy to avoid urate nephropathy and by maintaining a high fluid intake to help excrete light chains and calcium. In the event of acute renal failure, plasmapheresis is approximately 10 times more effective at clearing light chains than peritoneal dialysis, and acutely reducing the protein load may result in functional improvement. Urinary tract infections should be watched for and treated early. Chronic dialysis probably should not be initiated in patients who have failed to respond to antitumor therapy. Plasmapheresis may be the treatment of choice for hyperviscosity syndromes. Although the pneumococcus is a dreaded pathogen in myeloma patients. they do not respond to pneumococcal polysaccharide vaccines. The advent of intravenous gamma globulin preparations raises some hope that prophylactic administration may prevent some serious infections, but this has not been tested. Chronic oral antibiotic prophylaxis is probably not warranted. Patients developing neurologic symptoms in the lower extremities. severe localized back pain, or problems with bowel and bladder control may need emergency myelography and radiation therapy for palliation. Most bone lesions respond to analgesics and chemotherapy. but certain painful lesions may respond most promptly to localized radiation. The chronic anemia may respond to hematinics (iron. folate. cobalamin) and some have responded to androgens. The pathogenesis of the anemia should be established and specific therapy instituted. where possible.

WALDENSTRÖM'S MACROGLOBULINEMIA In 1948, Waldenstrom described a malignancy of lymphoplasmacytoid cells that secreted IgM. In contrast to myeloma, the disease was associated with lymphadenopathy and hepatosplenomegaly. but the major clinical manifestation was the hyperviscosity syndrome. The disease resembles the related diseases chronic lymphocytic leukemia, myeloma, and lymphocytic lymphoma. Waldenstrom's macroglobulinemia and IgM myeloma both follow a similar clinical course. The diagnosis of IgM myeloma is usually reserved for patients with lytic bone lesions and is important only because of the hazard of pathologic fractures.

The etiology of macroglobulinemia is unknown. The disease is similar to myeloma in being slightly more common in men and occurring with increased incidence with age (median, 64 years). There have been reports that the IgM in some patients with macroglobulinemia may have specificity for myelin-associated glycoprotein (MAG), a protein that has been associated with demyelinating disease of the peripheral nervous system and may be lost earlier and to a greater extent than the better known myelin basic protein in patients with multiple sclerosis. There is a surface antigen on natural killer cells that is cross-reactive with the MAG, and coincidentally, natural killer cells are decreased in multiple sclerosis. Sometimes patients with macroglobulinemia develop a peripheral neuropathy before the appearance of the neoplasm. There is speculation that the whole process begins with a viral infection that may elicit an antibody response that cross-reacts with a normal tissue component.

Like myeloma, the disease involves the bone marrow, but unlike myeloma, it does not cause bone lesions or hypercalcemia. Like myeloma, a serum M component is present in the serum in excess of 30 g/L (3 g/dL), but unlike myeloma, the size of the IgM paraprotein results in little renal excretion and only around 20 percent of patients excrete light chains. Therefore, renal disease is not common. The light chain isotype is kappa in 80 percent of the cases. Patients present with weakness, fatigue, and recurrent infections, similar to myeloma patients, but epistaxis, visual disturbances, and neurologic symptoms like peripheral neuropathy, dizziness, headache, and transient paresis are much more common in macroglobulinemia. Physical examination reveals adenopathy and hepatosplenomegaly, and ophthalmoscopic examination may reveal vascular segmentation and dilatation of the retinal veins characteristic of hyperviscosity states. Patients may have a normocytic, normochromic anemia. but rouleaux formation and a positive Coombs' test are much more common than in myeloma. Malignant lymphocytes are usually present in the peripheral blood. About 10 percent of macroglobulins are cryoglobulins. These are pure M components and are not the mixed cryoglobulins seen in rheumatoid arthritis and other autoimmune diseases. Mixed cryoglobulins are composed of IgM or IgA complexed with IgG, for which they are specific. In both cases, Raynaud's phenomenon and serious vascular symptoms precipitated by the cold may occur, but mixed cryoglobulins are not commonly associated with malignancy. Patients suspected of having a cryoglobulin based on history and physical examination should have their blood drawn into a warm syringe and delivered to the laboratory in a container of warm water to avoid errors in quantitating the cryoglobulin.

Control of serious hyperviscosity symptoms like an altered state of consciousness or paresis can be achieved acutely by plasmapheresis because 80 percent of the IgM paraprotein is intravascular. Aside from this, management is identical to that of myeloma. About 80 percent of patients respond to chemotherapy and their median survival is over 3 years. The absence of other serious organ toxicities results in a longer life span of patients with macroglobulinemia compared to those with myeloma.

HEAVY CHAIN DISEASES The heavy chain diseases are rare lymphoplasmacytic malignancies. Their clinical manifestations vary with the heavy chain isotype. They secrete a defective heavy chain that usually has an intact Fc fragment and a deletion in the Fd region. Gamma, alpha, and mu heavy chain diseases have been described, but no reports of delta or epsilon heavy chain diseases have appeared. Molecular biologic analysis of these tumors has revealed structural genetic defects that may account for the aberrant chain secreted.

Gamma heavy chain disease (Franklin's disease) This disease affects people of widely different age groups and countries of origin. It is characterized by lymphadenopathy. fever, anemia, malaise, hepatosplenomegaly, and weakness. Its most distinctive symptom is palatal edema, resulting from node involvement of Waldeyer's ring, and this may progress to produce respiratory compromise. The

diagnosis depends upon the demonstration of an anomalous serum M component [often <20 g/L (<2 g/dL)] that reacts with anti-IgG but not anti-light chain reagents. The M component is typically present in *both* serum and *urine.* Most of the paraproteins have been of the gamma, subclass, but other subclasses have been seen. The patients may have thrombocytopenia, eosinophilia, and nondiagnostic bone marrow. Patients usually have a rapid downhill course and die of infection; however, some patients have survived 5 years with chemotherapy.

Alpha heavy chain disease (Setigmann's disease) This is the commonest of the heavy chain diseases. It is closely related to a malignancy known as Mediterranean lymphoma. a disease that affects young people in parts of the world such as the Mediterranean. Asia, and South America in which intestinal parasites are common. The disease is characterized by an infiltration of the lamina propria of the small intestine with lymphoplasmacytoid cells that secrete truncated alpha chains. Demonstrating alpha heavy chains is difficult because the alpha chains tend to polymerize and appear as a smear instead of a sharp peak on electrophoretic profiles. Despite the polymerization. hyperviscosityis not a common problem in alpha heavy chain disease. Without J-chain–facilitated dimerization. viscosity does not increase dramatically. Light chains are absent from serum and urine. The patients present with chronic diarrhea. weight loss. and malabsorption and have extensive mesenteric and paraaortic adenopathy. Respiratory tract involvement occurs rarely. Patients may vary widely in their clinical course. Some may dcvclop diffuse aggressive histologies of malignant lymphoma. Chemotherapy may produce long-term remissions. Rare patients appear to have responded to antibiotic therapy, raising the question of the etiologic role of antigenic stimulation perhaps by some chronic intestinal infection.

Mu **heavy chain disease** The secretion of isolated mu heavy chains into the serum appcars to occur in a very rare subset of patients with chronic lymphocytic leukemia. The only features that may distinguish patients with mu heavy chain disease are the presence of vacuoles in the malignant lymphocytes and the excretion of kappa light chains in the urine. The diagnosis requires ultracentrifugation or gel liltration to confirm the nonreactivity of the paraprotein with the light chain reagents because some intact macroglobulins fail to interact with these serums. The tumor cells seem to have a defect in the assembly of light and heavy chains because they appear to contain both in thcir cytoplasm. There is no evidence that such paticnts should bc treated differently from other patients with chronic lymphocytic Icukemia.

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266 AMYLOIDOSIS

ALAN S. COHEN

DEFINITION AND CLASSIFICATION Amyloidosis may be defined as the extracellular deposition of the fibrous protein amyloid in one or more sites of the body. It was named by Virchow in 1854 on the basis of its color after staining with iodine and sulfuric acid. This protein has unique ultrastructural, x-ray diffraction. and biochemical characteristics. It can be deposited locally where it has no clinical consequences or may involve virtually any organ system of the body leading to severe pathophysiologic changes. or the disease may fall between these two extremes. The natural history of amyloidosis is poorly understood, and the clinical diagnosis is often not made until the disease is far advanced. It is now clear that there are multiple clinically and biochemically different forms of amyloid. that are so classified because of the unique fibrous structure that they all possess. The following classification is clinically the most useful: (1) primary (AL type) amyloidosis (no evidence for preexisting or coexisting disease); (2) amyloid associated with multiple myeloma (also AL type); (3) secondary or reactive (AA type) amyloidosis associated with chronic infectious diseases (e.g., osteomyelitis, tuberculosis. leprosy) or chronic inflammatory diseases (e.g., rheumatoid arthritis); (4) heredofamilial amyloidosis. a variety of neuropathic [AF transthyretin (prealbumin) type], renal, cardiovascular. and other syndromes, plus the amyloidosis associated with familial Mediterranean fever (AA type): (5) local amyloidosis (focal. oftcn tumorlike. deposits which occur in isolated organs, often endocrine. without evidence of systemic involvement): (6) amyloidosis associated with aging, especially in the heart and in the brain. and (7) amyloid associated with long-term hemodialysis. These clinical forms and their current biochemical classification are listed in Table 266-1.

PATHOLOGY AND STRUCTURE Amyloid is amorphous. eosinophilic. extracellular, and ubiquitous in distribution. The involved organs may have a rubbery consistency and a waxy, pink or gray appearance. Organ enlargement. especially of the liver, kidncy. spleen, and heart, may be prominent.

Microscopically, amyloid stains pink with the hematoxylin-eosin stain and shows metachromasia with crystal violet. The Congo red stain imparts a unique green birefringence when sections are viewed in the polarizing microscope. This is the single most useful procedure for establishing the presence of amyloid. Amyloid deposits may bc focal in almost any area of the body but are most often perivascular.

The heart may show focal or diffuse interstitial deposits in the myocardium, endocardium. or pericardium. In the aged heart, the atrium is usually focally involved or there may occur more diffuse lesions of the atria and ventricles. In the kidney, the glomerulus is primarily affected, although interstitial, peritubular, and vascular amyloid occur. In early lesions. small nodular or diffuse deposits appear near the basement membrane and, as the disease progresses. the glomerulus may be massively laden with amyloid. and its capillary bed will be occluded. In the gastrointestinal tract, there may be perivascular deposits only, or irregular or diffuse deposits may be found in the submucosa. in the muscularis mucosa, or subserosa. The amyloid may appear at any level or portion of the gastrointestinal tract including the gallbladder and pancreas. In the nervous system. amyloid has been described along peripheral nerves, in autonomic ganglia, and in senile plaques. in neurofibrillary tangles, as well as blood vessels ("congophilic angiopathy") of the central nervous system. It may be found in any portion of the orbit including the vitreous humor and cornea. In summary, there is virtually no area of the body that is spared. This ubiquitous distribution elicits a wide variety of clinical symptoms and signs.

All types of human amyloid consist of fine, nonbranching rigid fibrils that in tissue sections measure approximately 10×10^{9} m (100 Å) in diameter. Isolated amyloid fibrils have a delicate. thin.