MEDICAL GRAND ROUNDS

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MULTIPLE MYELOMA

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I. NORMAL IMMUNOGLOBULINS AND MYELOMA PROTEINS

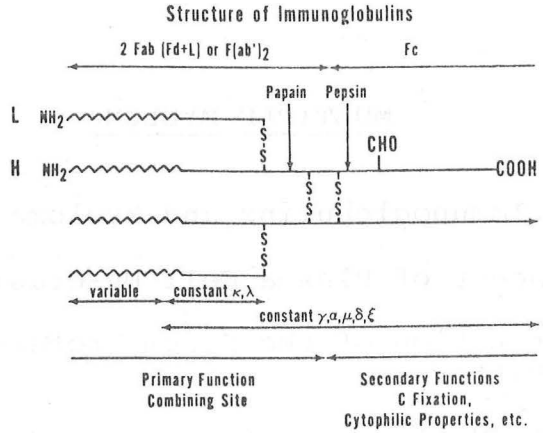


FIG. 1. Schematic diagram of immunoglobulin molecules and localization of structures responsible for primary and secondary functions of antibodies. H = heavy chain; L = light chain; CHO = carbohydrate. (1)

Normal immunoglobulins are produced via the proliferation and differentiation of antigen-reactive B lymphocytes into plasma cells. These heterogeneous immunoglobulins possess antibody activity and are the effectors of humoral immune responses.

The principal features of immunoglobulin structure (Fig 1) can be summarized as follows (1-3):

1) All immunoglobulins have a common fundamental four-chain structure consisting of two light (L) polypeptide chains (molecular weight about 23,000 daltons) linked by disulfide bonds to two heavy (H) chains (molecular weight about 50,000 to 70,000 daltons). In general, each plasma cell synthesizes and secretes one class of H chain and one class of L chain at any one time during its lifespan.

2) All immunoglobulins contain a "hinge" region in the area of the interheavy chain disulfide bridges which is uniquely susceptible to proteolytic enzymes (e.g., papain, pepsin, trypsin); brief exposure to such enzymes results in cleavage of the molecule into large fragments which are functionally distinct. The amino-terminal (N-terminal) part of the heavy chain, together with the entire light chain, is termed the Fab fragment, which contains a single antigen-binding site. The carboxyl-terminal (C-terminal) portions of heavy chains make up the Fc fragment, a region

of the molecule in which the amino acid sequence tends to be constant and, thus, contains many of the features common to individual immunoglobulin classes. The hinge region in the middle of the molecule also may act as a swivel point allowing for limited flexibility of the Fab regions on combination with antigen.

3) The five human immunoglobulin classes (IgG IgA, IgM, IgD and IgE) are defined by structural differences in their heavy chains (γ, α, μ, δ, and ε, respectively). These may be delineated by the use of appropriate antisera specific for each chain.

4) The two light chain types (kappa and lambda) are common to all the heavy chain classes. Normally, the serum (or urine) κ:λ ratio is about 2:1, but any single immunoglobulin molecule is symmetric, i.e., it bears either κ or λ light chains.

5) The amino-terminal (variable) portions of both heavy and light chains contribute to the antibody site. Amino acid sequence, X-ray crystallographic and affinity labeling studies all suggest that three short "hypervariable" regions are present in V_L and V_H and appear to form the actual combining site for antigen; these hypervariable regions on each Fab fragment are brought into close proximity in the three-dimensional structure of immunoglobulin molecules and are in contact with bound antigen. Computer-generated profiles show similar patterns of hypervariable regions on all L chains and H chains for which sequence data are available, whether the chains are derived from myeloma proteins or from antibodies of defined but differing specificities. It thus appears that in all immunoglobulins, there is one combining site per heavy-light chain pair (i.e., one per Fab). Antibody specificity is determined by the primary amino acid sequence (and thus the genetic code) of the variable portions of each chain. It follows, therefore, that antibodies having different specificities differ in primary amino acid sequence. Such structural and functional diversity is unique to this family of proteins; the precise mechanism for its generation is unclear. Individual specificity (idiotypy) refers to the fact that each immunoglobulin molecule bears unique antigenic determinants; these are located on the V regions. It should be pointed out that most commercially available antisera are directed to determinants on the constant regions of H and L chains; these reagents cannot recognize the variable regions.

6) Structural and functional subunits (domains, homology regions) have been recognized within each intact polypeptide chain. These domains (Fig 2)are characterized by the following features: a) length of 110 to 120 amino acid residues; b) the presence of an intrachain disulfide loop linking about 60 residues; and c) homology in amino acid sequence.

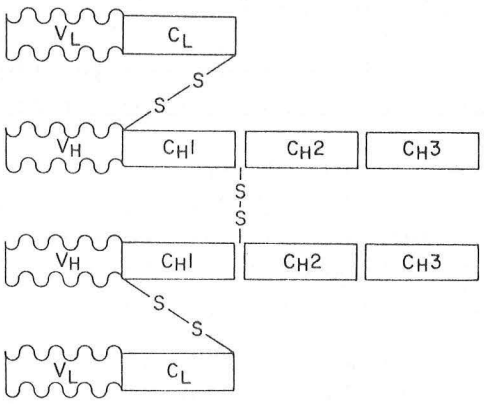


Fig. 2. Homology regions in immunoglobulins. The abbreviations V_L and V_H denote the variable regions of light and heavy chains, respectively, and C_L and C_H the constant regions. The μ and ϵ heavy chains have a fourth constant domain (C_H4) (3)

Domains also differ in such biologically important properties as antigen binding, complement fixation and cytophilic properties. Although light chains have only 2 domains (V_L and C_L), heavy-chain classes are not uniform in homology from domain to domain and appear to have evolved with different mutation rates but with conservation of essentially structural features. Hence individual domains rather than whole chains should be compared with respect to function and evolution. Chemical and X-ray diffraction studies suggest that the domains are compact, tightly folded globular units connected by rather flexible segments to polypeptide chains that are exposed to solvent and enzymatic attack. Immunoglobulin domains also have been recognized to be homologous with β_2-microglobulin, a polypeptide chain (MW $\sim$ 11,800 daltons) which is believed to be a subunit of HL-A histocompatibility antigens.

7) A small (MW $\sim$ 15,000 daltons) nonimmunoglobulin polypeptide component is found in polymeric immunoglobulins (IgM and IgA). This J (joining) chain appears to be required for polymerization of these molecules. It is synthesized by the same plasma cell that produces the immunoglobulin molecule to which it is bound and is probably added on just before release from the cell. The J chain is bound by disulfide bridges to the Fc portion of the H chain. Only one J chain is present on each polymer of IgA or pentamer IgM. J chains are not present in IgG or monomer IgA.

In addition to the five major classes of human immunoglobulins, subclasses with unique H-chain antigenic determinants have been identified. Thus normal IgG contains four subclasses (IgG1, IgG2, IgG3 and IgG4) and IgA contains two subclasses (IgA1 and IgA2) (Fig 3).

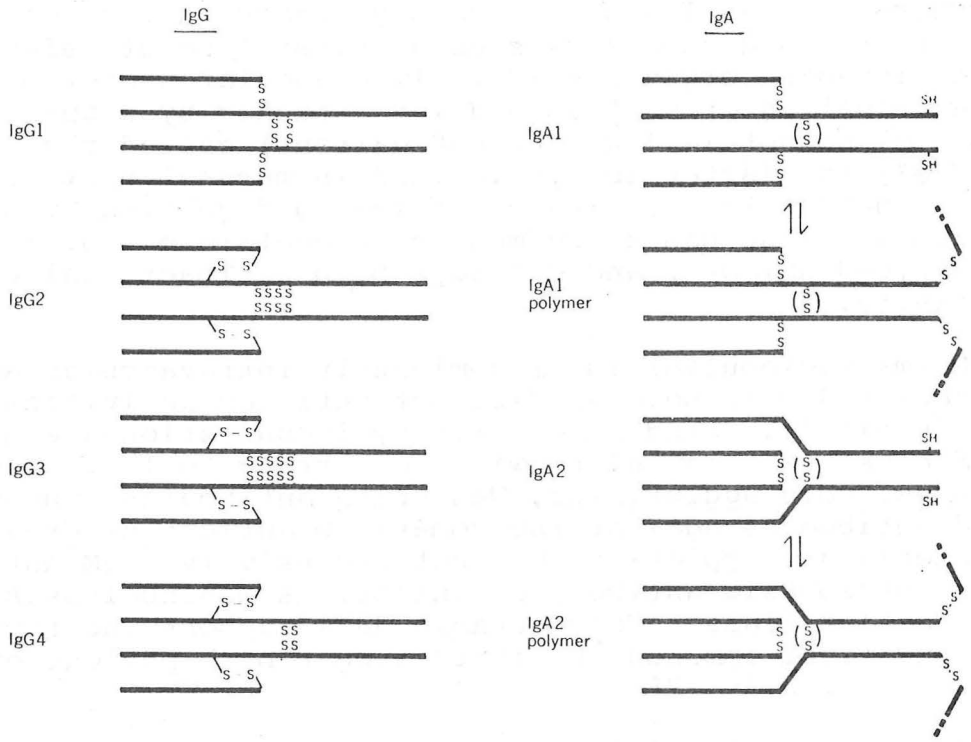


Fig. 3. Topological models of human IgG and IgA isotypes. (4)

Similar class heterogeneity may exist for IgM, IgD, and IgE. Subclasses have also been recognized in each of the two types of L chains. The properties and biologic activities of human immunoglobulins are summarized in Table 1.

TABLE 1. Properties of Human Immunoglobulins (5)

	IgG1	IgG2	IgG3	IgG4	IgA	IgM	IgD	IgE
Serum concentration (mg/ml)	5-12	2-6	0.5-1	0.2-1	0-2.5	0.5-1.5	0-0.4	0-0.002
Electrophoretic mobility	γ	γ-β	γ	γ-β	β	β-γ	γ-β	γ-β
Svedberg coefficient	6.6S	6.6S	6.6S	6.6S	7S°	18S	6.5S	7.9S
Heavy chains	γ_1	γ_2	γ_3	γ_4	α	μ	δ	ϵ
Light chains (κ/λ ratio)	2:1	1:1	1:1	5:1	1:1	3:1	1:4	
Half-life (days)	23	23	7	23	6	5	3	2
% Intravascular	45	45	45	45	42	76	75	
Placental transfer	+	+	+	+	0	0	0	0
Complement fixation†	++	+	++	0	0	+	0	0
PCA reactivity‡	+	0	+	+	0	0	0	0
P-K reactivity§	0	0	0	0	0	0	0	+
Macrophage binding	+	±	+	±	0	0	0	0

° Some IgA molecules 9S, 11S, and 13S.
† Classic complement pathway.
‡ Passive cutaneous anaphylaxis.
§ Prausnitz-Küstner.

IgG accounts for approximately 75% of the immunoglobulins in normal serum. IgG is also the only class which is transferred across the placenta and in which catabolic rate is influenced by the serum level (6).

IgA is the principal immunoglobulin present in secretions (gastrointestinal and respiratory tracts, urine, colostrum and tears) and thus serves as a "first line of defense" to many invading organisms (7). In glandular secretions, secretory IgA (SIgA) is present as a dimer attached by disulfide bonds to a glycoprotein (MW $\sim$ 60,000 daltons) called the "secretory piece"; the latter is synthesized in mucosal epithelial cells and enhances the resistance of IgA to digestion by proteolytic enzymes. SIgA has a sedimentation coefficient of 11S (MW $\sim$ 390,000 daltons) and displays both antibacterial and antiviral activity.

IgM (macroglobulin) is predominantly intravascular and is associated with several distinct antibody activities. The initial antibodies detected after primary immunization are usually of the IgM class, with a later switch occurring to IgG. Isohemagglutinins, cold agglutinins, Wasserman antibodies, rheumatoid factors and antibodies against the somatic O antigen of Gram-negative bacteria are typically, but not exclusively, IgM antibodies. The heterophile antibody of infectious mononucleosis also belongs to the IgM class. Considerable data support the fact that IgM is the first immunoglobulin to appear both phylogenetically and ontogenetically (2).

The precise role of IgD is unclear although surface IgD molecules have been noted, along with IgM, on B lymphocytes from normal individuals, as well as on those from patients with chronic lymphocytic leukemia and macroglobulinemia (8).

IgE mediates immediate-type hypersensitivity (Type I); combination of antigen (allergen) with cell-fixed IgE antibody leads to the release of multiple vasoactive molecules responsible for many manifestations of the allergic (reaginic) response (9). Serum IgE levels are frequently elevated in patients with extrinsic asthma, hay fever and parasitic infestations.

Light Chains and Bence Jones Proteins

The proteins excreted in the urine of patients with multiple myeloma were originally studied by Dr. Henry Bence Jones, a London physician, 130 years ago and thus were among the first proteins described (10). Bence Jones found that the urine of a patient with myeloma precipitated when heated, cleared when boiled, but reprecipitated when cooled; he concluded that this unusual protein was the "hydrated deutoxide of albumin."

During the next century, numerous attempts were made to define the nature of Bence Jones proteins (over 700 papers appeared on the subject). However, they remained a biochemical curiosity except in the realm of clinical medicine: the demonstration of Bence Jones protein (BJP) established the diagnosis of multiple myeloma and this finding was said to be present in approximately half the patients with this disorder.

In 1962, Edelman and Gally (11) demonstrated that the L chains prepared from a serum IgG myeloma protein had identical properties (molecular weight, electrophoretic, thermo-solubility and spectrofluorometric) as those of the BJP isolated from the same patient's urine. Subsequently, the same investigators showed that free monoclonal L chains (BJP) exist as both monomers (MW $\sim$ 23,000 daltons) and dimers (MW $\sim$ 45,000 daltons). Type kappa (κ) chains exist mainly as monomers but may be present as dimers; type lambda (λ) chains occur as covalently-linked dimers. The classic reversible thermal solubility property as well as "amyloidogenic" characteristics are associated with the variable (V_L) half of the molecule (12).

BJP are synthesized de novo and are not degradation products of the complete Ig in the serum. A slight excess of light chains is produced normally and small amounts of free polyclonal κ and λ chains (up to 40 mg/24 hr) are present in the urine of normal subjects. Both free polyclonal L chains and monoclonal BJP are catabolized by the proximal renal tubular cells (12).

Genetic Markers (Allotypes) and Allelic Exclusion

As is true with other serum proteins, immunoglobulin chains exhibit various genetic markers (allotypes). These serologically-detected inherited antigenic determinants are due to specific amino acid substitutions in the constant regions of the polypeptide chains. Examples include the various Gm markers on gamma chains and the InV marker on kappa chains (13). Studies on Ig allotypic markers have shown that in heterozygotes, only one of the two alternative markers is expressed on each mature plasma cell. Thus no single cell will make antibody molecules of more than one phenotype. Because structural genes for Igs are not sex-linked, these genes presented the first example of allelic exclusion of autosomal chromosomes in humans. The mechanism of this intriguing immunogenetic phenomenon is unclear.

In summary, immunoglobulins differ from all other proteins in their variability, their heterogeneity, their genetic control and their antibody specificity. Much of our current knowledge about normal immunoglobulin structure, genetics, synthesis and metabolism has been extablished by the study of myeloma proteins; they have been invaluable in these investigations principally because of their availability in large amounts and their homogeneous nature. At the clinical level, characterization of

these proteins is critical to diagnosis and management of patients in whom they are found. These and other advances attributable to the study of myeloma proteins are listed in Table 2.

TABLE 2

Results, Research Tools, and Practical Applications Derived from Basic Research on Bence Jones Proteins, Myeloma Globulins, and Macroglobulins (3)

1. Clinical test for Bence Jones proteinuria in the diagnosis of multiple myeloma; modification of the heat test
2. Elucidation of the aberration of protein synthesis in multiple myeloma, macroglobulinemia, and related diseases
3. Identification of κ and λ light chains in normal immunoglobulins; quantitation of normal immunoglobulins
4. Classification of normal "γ-globulin" into IgG, IgA, IgM, IgD and IgE; quantitation of normal abundance
5. Principles of structure of antibodies
6. Amino acid sequence diversity of antibodies and immunoglobulins; theories of genetic control of antibody biosynthesis
7. Models for X-ray analysis of antibody binding sites
8. Antisera for detection and quantitation of Ig types in hypergammaglobulinemia in many diseases and in hereditary hypogammaglobulinemia and agammaglobulinemias
9. Antisera for routine quantitation of Ig types in plasma proteins by automated immunoprecipitation
10. Antisera for cellular localization of antibodies
11. Antisera for detection of surface receptors on immunocytes for study of antibody biosynthesis
12. Immunogenetics—discovery of genetic differences in immunoglobulins of possible value in transfusion reactions and organ transplantation
13. Immunogenetics—applications to population genetics, forensic medicine, and evolution of immunoglobulins
14. Discovery of normal IgE and its function as the skin-sensitizing antibody; quantitative radioimmunoassay (RIA) and radioallergosorbent test (RAST)
15. Identification of Bence Jones protein as the paramyloid protein causing primary amyloidosis
16. Nature of antibody-mediated autoimmune reactions, e.g., rheumatoid factor IgM as the antibody to IgG
17. Binding site of complement; conformational changes
18. Cellular system for study of mutation and clonal variation
19. Subcellular study of protein biosynthesis and mutation
20. Animal and cellular models for clonal restriction and cellular differentiation

II. THE CONCEPT OF PLASMA CELL DYSCRASIAS (PCD)

Definition: A group of clinically and biochemically diverse disorders characterized by the disproportionate proliferation of one clone of cells normally engaged in immunoglobulin synthesis, and the presence of a structurally and electrophoretically homogeneous (monoclonal) immunoglobulin or polypeptide subunit in serum or urine. The disorders vary from asymptomatic and apparently stable conditions to progressive, overtly neoplastic disorders such as multiple myeloma. The classification of plasma cell dyscrasias is given in Table 3. Both clinical and immunochemical criteria must be used to diagnose these disorders (14, 15).

TABLE 3. Plasma Cell Dyscrasias (5)

Clinically overt (symptomatic) forms:
Multiple myeloma (IgG, light chain disease, IgA, IgD, IgE, nonsecretory)
Macroglobulinemia (IgM)
Primary amyloidosis (usually Bence Jones protein)
Heavy chain diseases (γ, α, μ)
Lichen myxedematosus (papular mucinosis) (IgG)
Clinically occult (asymptomatic or presymptomatic) forms:
Plasma cell dyscrasias of unknown significance (PCDUS)
With chronic infectious or inflammatory processes
With nonreticular neoplasms
With various other disorders
In healthy persons (age-related incidence)
Transient plasma cell dyscrasias
With infections
With drug reactions
With cardiac surgery

The cause of the PCDs is unknown. Most of the monoclonal immunoglobulins (M-components) synthesized by plasma cells are not qualitatively abnormal; rather, they appear to be the normal products of a single clone of cells that has undergone intense proliferation (16). Some of these M-proteins show antibody activity, most frequently directed toward autoantigens, bacterial antigens or haptens (Section IX). Serum levels of normal immunoglobulins are commonly reduced.

The normal structural features of immunoglobulin molecules and the development of the major immunoglobulin classes have been discussed. Normal plasma cell production of immunoglobulins is heterogeneous, with individual clones of plasma cells producing the different immunoglobulins (IgG, IgM, IgA, IgD, or IgE) (Fig 4). Each plasma cell clone secretes only one class of heavy chain (γ, μ, α, δ, or ε) and one class of light chain (κ or λ) at any one time in its lifespan.

A disproportionate proliferation of one clone results in a corresponding increase in serum levels of its secreted molecular product (Fig 4). This monoclonal immunoglobulin (the M-component) is readily detected by finding a tall symmetric spike with α-2, β or γ mobility on cellulose acetate electrophoresis of serum or urine, but immunoelectrophoresis (IEP) is required to identify the heavy and light chain class of the protein. The magnitude of M-component is related to the number of cells in the body producing that component; these proteins are thus valuable markers in diagnosis and management of patients with PCDs.

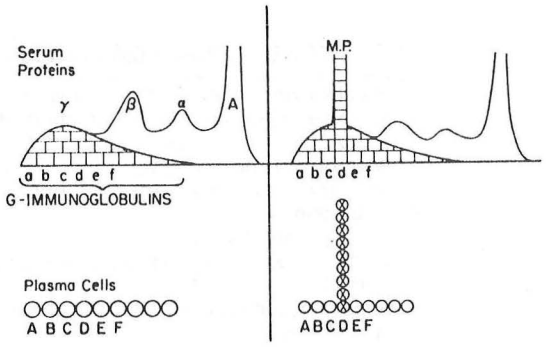


Fig 4. Schematic representation of normal (left panel) and monoclonal (right panel) marrow plasma cell proliferation. Upper portions of each panel show resulting serum protein electrophoretic (SPE) patterns. Note the homogeneous, monoclonal protein (M.P.) component in the SPE pattern on right (14).

Most commonly, serum M-components are found in patients with malignant PCD (multiple myeloma, Waldenstrom's macroglobulinemia, primary systemic amyloidosis, or the various heavy chain diseases). Serum M-components without evidence of malignant PCD are also found in association with a variety of other diseases and in a few asymptomatic, apparently healthy persons; the incidence is age-related -- 1% of persons age 25 and 3% of those age 70. Although many asymptomatic cases remain unchanged for years and are therefore seemingly benign, others represent incipient or "premyeloma" fortuitously discovered on routine SPE. It is impossible to predict the course in any individual patient, and clinically symptomatic myeloma may not evolve for as long as 20 years (17,18). The designation "plasma cell dyscrasia of unknown significance" (PCDUS) is therefore preferred for asymptomatic individuals with monoclonal serum components.

Patients with PCDUS usually have low levels of M-component that are stable with time, and show mild marrow plasmacytosis, normal levels of serum immunoglobulins, and no lytic bone lesions or Bence Jones proteinuria (Section VII).

III. INTERPRETATION OF THE SPE PATTERN

During the past decade, electrophoresis of serum on cellulose acetate has become routinely available in most hospital and clinical laboratories (19). This development has led to the previously noted finding that many patients and some normal individuals have homogeneous M-components.

Normal human serum contains over 100 individual proteins, each having a specific function (20). The normal concentrations of these proteins vary over a wide range (∿ 6 logs) from a few micrograms to several grams per dl. In addition to immunoglobulins, serum proteins function as enzymes, proteinase inhibitors, complement components, kinin precursors, and transport substances for vitamins, hormones, lipids and metals. The major components in the various fractions of the normal SPE pattern are listed in Table 4.

Table 4. Major Constituents of the SPE Fractions

-(Cathode)				+(Anode
γ-Globulin	β-Globulin	α_2-Globulin	α_1-Globulin	Albumin
IgG	β-Lipoprotein	α_2-Macroglobulin	α_1-Antitrypsin	Albumin
IgA	Transferrin	α_2-Lipoprotein	α_1-Lipoprotein	
IgM	Plasminogen	Haptoglobin	α_1-Acid glycoprotein	
IgD	Complement	Ceruloplasmin	(orosomucoid)	
IgE	Hemopexin	Erythropoietin		

Modified from (21)

Immunoglobulins may migrate anywhere from the slow (cathodal) gamma to the alpha-2 globulin area (Fig 5).

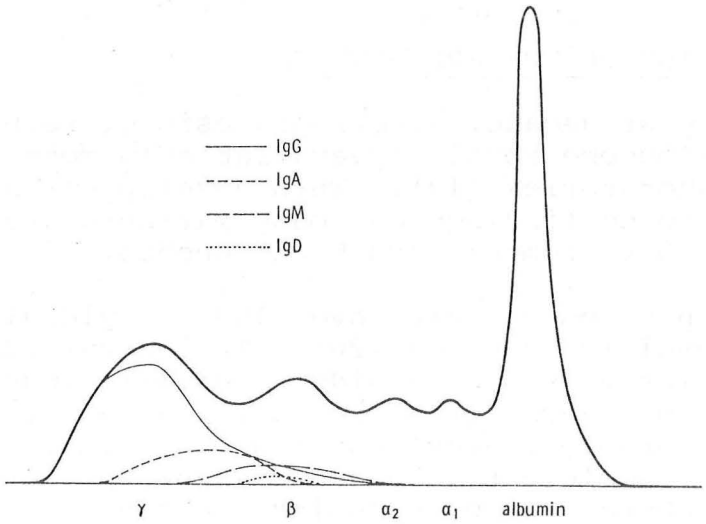


Fig. 5 .Distribution of four human immunoglobulins on electrophoresis of serum. The IgE class has a similar mobility to IgD but cannot be represented quantitatively because of its low level in serum. (22)

Tips on interpretation of the SPE pattern

1) Normal values in most laboratories: albumin 3.8-5.0 g/dl, α_1, $\sim$ 0.2 g/dl; α_2 $\sim$ 0.8 g/dl; β $\sim$ 0.9 g/dl; γ $\sim$ 1.2 g/dl.

2) For recognition of M-proteins, contour of the pattern is more important than quantification of the various fractions.

3) Whenever possible, examine the stained membrane for presence of a discrete, homogeneous M-component rather than relying solely on the densitometric tracings (esp valuable for determining application artifacts).

4) M-components are best recognized by SPE; however, they must be identified by immunologic methods (IEP).

5) Is hypogammaglobulinemia (γ < 0.6 g/dl) present? If so, this should be confirmed by IEP and quantification of serum Ig levels by radial immunodiffusion (RID). Careful examination of the urine for BJP should be performed; IEP best.

6) Quantification of typical, narrow church-spire M-components is best done from the SPE pattern. Increases in Ig levels are notoriously unreliable by RID (esp true for polymeric M-proteins - IgA and IgM).

7) A decrease in albumin and increase in alpha-2 globulin are nonspecific findings and are present in many inflammatory processes and chronic diseases. Most alpha-2 "spikes" are not due to Ig M-components but a few are - confirm with IEP.

8) IgA M-proteins often appear relatively heterogeneous (i.e., broadbased) due to polymer formation or differences in carbohydrate content; IgD M-proteins may have a similar appearance or may be present in such a low quantity that they are scarcely evident on the pattern. Whenever these are possibilities or when it is difficult to distinguish such situations from polyclonal (diffuse) hypergammaglobulinemia, IEP with monospecific heavy and light-chain antisera should be performed.

9) Bence Jones proteinemia is rarely evident on SPE but can often be identified by serum IEP. The most likely cause of a "double spike" is retained BJP in a patient with renal failure who also has an intact M-protein molecule.

10) a) Gross hemolysis-large, often broad, α-2 peak (Hgb-Hp complexes)

b) Hyperlipidemia - α-2 or β peak

c) Plasma - homogeneous component in slow-β region (fibrinogen)

d) Marked Fe deficiency anemia - homogeneous β component ($\uparrow\uparrow$ transferrin) (very rare)

IV. MULTIPLE MYELOMA (PLASMA CELL MYELOMA; MYELOMATOSIS)

Definition: A progressive neoplastic disease characterized by marrow plasma cell (or secretory B cell) tumors and overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD, IgE) or Bence Jones protein (free monoclonal κ or λ light chains), and often associated with numerous osteolytic lesions, hypercalcemia, anemia, renal damage, and increased susceptibility to bacterial infections. Persons over the age of 40 are most commonly affected.

Criteria for diagnosis (23):

A: Demonstration of an M-protein in serum and/or urine

B1: Marrow plasma cells in sheets or clusters (i.e., marrow plasma cell tumors)

B2: Osteolytic lesions (unassociated with metastatic carcinoma or granulomatous disease)

B3: Bence Jones proteinuria in excess of 300 mg/day

Diagnosis of myeloma

= A plus any one of the categories in B
= B1 plus B2 (for "nonsecretory" cases; < 1% of all myeloma)

V. CLINICAL AND LABORATORY FINDINGS; CELL KINETICS AND STAGING

Multiple myeloma is the prototype "overt" or symptomatic PCD and, as noted, can be characterized according to the type of homogeneous immunoglobulin produced by the neoplastic clone of plasma cells (21,24,25). Myeloma accounts for approximately 1% of all malignancy and 10% of hematologic malignancies (26). The annual incidence is 2 to 4 per 100,000 population (25). Several studies suggest that myeloma is more common in black than white persons (27); men and women are equally affected. The disorder has been reported in spouses (28-30), mother and daughter (31), and family and community "clusters" (32,33), but these are very rare. The usual patient is over 40 years of age (mean 62), although occasional reports of individuals in their teens or twenties have appeared (34-37). Myeloma patients are said to have an increased incidence of other neoplasms but this is questionable (38).

Symptoms and signs. The usual mode of clinical presentation is in one of three ways: 1) The most common presentation relates to the presence of bone pain, especially in the spine, pelvis or ribs. 2) Less frequently, patients manifest renal failure of unknown etiology; this is particularly common in the "light chain disease" subgroup (see Case 1). 3) Finally, patients may present because of the recent onset of recurrent bacterial infections - especially pneumococcal pneumonia (39). Aside from the inconstant presence of bone tenderness, physical examination is usually non-revealing. Pallor may be noted if anemia is severe. Lymphadenopathy and hepatosplenomegaly (40) are notably absent unless the patient has amyloid. Occasional patients present with signs of cord compression (23).

Laboratory findings. A mild to moderate normocytic-normochromic anemia is usually present, although hypochromic-microcytic red cell morphology may be present if the patient has a coexisting iron reutilization defect ("anemia of chronic disease"), iron deficiency anemia, or sideroblastic state (41-43). The direct Coombs test is negative if the cells are thoroughly washed. Occasional plasma cells may be evident on careful examination of the blood smear but this finding is nonspecific (44-48). True plasma cell leukemia (49-57) is uncommon (see Case 2). Plasma cells also may be found in the urine (58). Except for the "light chain disease" (LCD) subgroup, rouleau on peripheral smear and an ESR in excess of 100 mm/hr are helpful early laboratory findings which frequently suggest the underlying disorder (23). Leukocyte and platelet counts are usually normal at the time of diagnosis (23,59). Leukocyte alkaline phosphatase levels have been reported to be elevated in 60 of 62 patients with myeloma (60).

As noted, the presence of a plasma cell dyscrasia is most readily identified by the finding of a narrow band on cellulose acetate electrophoresis of serum or urine. It is important to emphasize that both serum and urine must be analyzed electrophoretically and immunoelectrophoretically if a precise immunochemical diagnosis is to be made, since about 25% of myeloma patients have LCD, an entity in which only free homogeneous light chains (Bence Jones proteins) are secreted by the abnormal monoclone (23,61). Because Bence Jones proteins are small molecules, they are usually filtered by the glomeruli and excreted in the urine but do not accumulate in serum unless renal failure supervenes. Thus one cannot rely on the absence of an M-spike in serum to rule out multiple myeloma (Fig 6). Approximately 99% of myeloma patients have a demonstrable M-protein if both serum and urine are analyzed by electrophoretic and immunoelectrophoretic techniques (Table 5) (23,26,61,62). Intracellular M-protein often can be demonstrated by immunofluorescence studies in the rare nonsecretory variant (63-70). Sheets or clusters of marrow plasma cells and the presence of osteolytic lesions will identify such patients. In approximately half of patients with localized plasmacytoma, an M-component may not be present initially. In addition to bone (23,71), plasmacytomas have been described in the stomach, small and large intestine, nasopharynx, skin and subcutaneous tissues, breast, liver, spleen, lymph nodes, testis, thyroid, kidney, lung, heart, brain and meninges (72-90). True plasmacytomas must be differentiated from reactive plasma cell infiltrates (91-93).

About half of myeloma patients will have monoclonal IgG serum proteins (Table 5). In our experience, 26% of myeloma patients (18% of all patients with PCD) produce only Bence Jones protein and, therefore, have LCD (23). This large subgroup of patients tends to be more difficult to diagnose, since such individuals usually have no evidence of an M-spike in serum (instead they generally display hypogammaglobulinemia) and tend not to have rouleau on peripheral smear. Identification and characterization

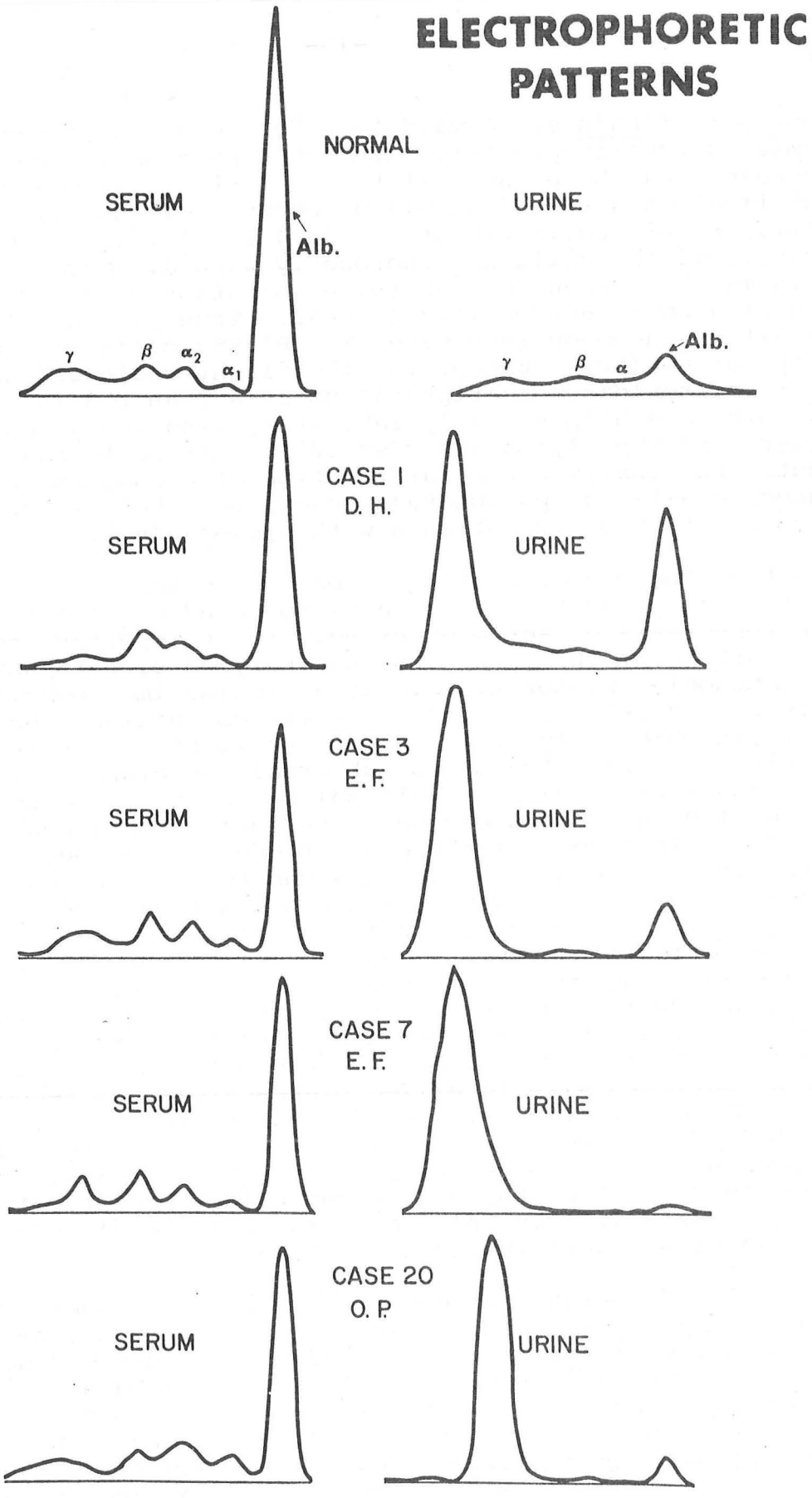

ELECTROPHORETIC PATTERNS
NORMAL
SERUM
URINE
Alb.
γ
β
α2
α1
α
Alb.
CASE 1
D. H.
SERUM
URINE
CASE 3
E. F.
SERUM
URINE
CASE 7
E. F.
SERUM
URINE
CASE 20
O. P.
SERUM
URINE

Fig. 6

TABLE 5. Types of M-proteins in Myeloma

	Hobbs(62)	Osserman(61)	Kyle(26)	Dallas Series*
#Cases	212	351	537	217
IgG	53%	52	59	53
IgA	25	22	23	19
IgD	1	1	1	1
BJ only (LCD)	19	25	(17)	26
Biclonal	2	<1	-	-
No M-protein	-	-	<1	<1

*During the interval 1969-74, a total of 327 patients with plasma cell dyscrasias were identified. Approximately 30% of those with IgG and 20% with IgA M-proteins did not have evidence of myeloma. Eleven per cent of the total population had macroglobulinemia. None of these subgroups is included in the table above (see 23).

of proteinuria thus becomes especially critical to the diagnosis of these myeloma patients (Fig 6). LCD also is important to recognize because patients with this entity have a higher incidence of renal functional impairment and amyloidosis than other myeloma patients (Section VI). Approximately 20% of patients with myeloma have IgA proteins; these often appear relatively heterogeneous (i.e., broadbased) on SPE due to polymer formation or differences in carbohydrate content. L-chain typing tends to be difficult in patients with monoclonal IgA proteins unless Bence Jones proteinuria is also present (24,94). IgD accounts for only 1% of myeloma proteins; a typical M-spike may not be evident on SPE and λ L chains are present in 80-90% of cases (95). Only a few cases of IgE myeloma have been reported (96,97).

Approximately 70% of the entire group of myeloma patients will have Bence Jones protein identifiable in urine by sensitive electrophoretic and immunochemical techniques. Bence Jones proteins also may be demonstrable in serum in a smaller proportion of patients (23).

Detection of Bence Jones protein. The clinician must bear in mind that all proteinuria is not albuminuria and that identification of abnormal proteinuria requires that the components be quantified and characterized by means of 24-hour urine protein excretion, cellulose acetate electrophoresis (UPE) and IEP. A variety of screening tests to identify significant proteinuria are utilized in most laboratories. The commonly employed Dipstix method does not recognize most urine Bence Jones proteins (23,24). Thus it has been frequent in our experience to obtain a negative protein by Dipstix in the face of 5 grams or more of Bence Jones proteinuria per 24 hours. The classic heat precipitation test for BJP is obsolete, insensitive and cumbersome to perform. As has been pointed out previously, the results of the heat test as carried out in most hospital laboratories often are actually misleading (71). For the past nine years, we have screened for urine protein, including Bence Jones, by utilizing both the sulfosalicylic acid (SSA) and p-toluene sulfonic acid (TSA) methods (23). SSA will precipitate Bence Jones, as well as other urine proteins, if present in a concentration exceeding approximately 30 mg/dl. TSA is particularly useful in initial screening for BJP since this reagent does not precipitate albumin when the latter is present in concentrations as high as 25 gm/dl (98). It should be pointed out that TSA is not specific for Bence Jones proteins or even for polyclonal immunoglobulin light chains; this reagent will precipitate other plasma proteins found in urine, especially transferrin (99). However, combined use of the SSA and TSA tests has provided a simple, quick and inexpensive method of screening urine specimens

for Bence Jones protein. The diagnosis of LCD is particularly revealing in this regard. As noted, these myeloma patients ordinarily do not have serum M-spikes, rouleau, or markedly elevated ESR's. Because the Dipstix urine protein is frequently negative, the diagnosis of myeloma is often missed because appropriate screening tests for detection of Bence Jones protein are not employed.

Quantitative determination of 24-hour urine protein excretion is important in any patient with Bence Jones proteinuria because its presence may be an adverse prognostic factor in certain patients and because criteria for objective response to therapy rest, in part, on the demonstration of a 50% or greater decrease in serum or urine M-protein (100,101). It may be necessary to concentrate the urine prior to performance of cellulose acetate electrophoretic or immunoelectrophoretic analyses. This can be accomplished conveniently through the use of Minicon B15 concentrators after the appropriate concentrating factor is determined by initial screening with SSA and TSA. UPE will then disclose the proportion of albumin which is present, as well as documenting the presence of a tall narrow monoclonal spike in the beta, gamma or alpha-2 region (Fig 6). The components can then be typed for L chain class by the use of IEP.

Normal protein excretion is less than 200 mg/24 hr. Approximately 5 to 40 mg of this "normal" proteinuria consist of free immunoglobulin L chains but these are polyclonal (i.e., heterogeneous) and present in the usual $\kappa:\lambda$ ratio of 2:1. In the patient with nephrotic syndrome, the SSA test will be 4+ and the TSA test will usually be negative or only slightly positive, while UPE will disclose a pattern which appears similar to that of serum. IEP of urine from such a patient will disclose multiple-component proteinuria, predominantly albumin; various other serum proteins will be present and, usually, both κ and λ L chain determinants will be detected.

By contrast, in the patient with Bence Jones proteinuria, both the SSA and TSA tests tend to be strongly positive. As noted, UPE and urine IEP confirm the presence of free monoclonal L chains. Except in the patient who has coexisting amyloidosis, significant albuminuria does not occur in patients with myeloma. Thus the presence of marked albuminuria in addition to Bence Jones protein should alert the physician to the probable presence of glomerular amyloid (23,102).

A few patients with Bence Jones proteinuria but without other evidence of myeloma or primary amyloidosis have been reported (103-105) but the incidence of such nonmyelomatous Bence Jones proteinuria is extremely low. In general, the demonstration of significant (i.e. > 300 mg/24 hr) Bence Jones proteinuria

is a reliable, albeit not absolute, indication of malignancy in patients with plasma cell dyscrasias (23,106).

Bone marrow findings. The average marrow aspirate from a patient with multiple myeloma contains 30-35% plasma cells (normal < 5%) (26,107). However, it is also true that a normal marrow is consistent with the diagnosis of myeloma. Occasionally, the aspirate may be hypocellular and simulate aplastic anemia (108); in such instances a core biopsy should be obtained. Marrow involvement tends to be patchy, especially in the early phases of the disease. Consequently, the specimen obtained may show no definite increase in plasma cells or, alternatively, only mild plasmacytosis (23,109). Since many chronic diseases associated with ongoing immune responses are also associated with marrow plasmacytosis (e.g., rheumatoid arthritis, tuberculosis, ulcerative colitis)(110), we feel it is usually necessary to demonstrate sheets or multiple clusters (greater than 10 per oil immersion field) of plasma cells in order to make the diagnosis of a malignant plasma cell dyscrasia (23). This approach to histologic diagnosis, therefore, rests on the demonstration of marrow plasma cell tumors rather than on any attempt at cytologic differentiation between normal and malignant plasma cells (109,111). Although there is no question that some myeloma patients have marrow plasma cells which are so anaplastic as to be clearly malignant, this is the exception. In most situations it is difficult to distinguish normal from malignant plasma cells, despite the claim of some investigators that nuclear-cytoplasmic dissociation as determined by electron or light microscopy can be helpful in this regard (112,113).

Similarly, it should be emphasized that one cannot reliably determine the immunoglobulin abnormality from plasma cell morphology (23,109, 111,114). Identification of the type of associated M-protein production is an immunochemical diagnosis and not a histologic one.

Many different types of inclusions have been described in plasma cells from normal individuals and myeloma patients. Russell bodies are intracytoplasmic hyaline, acidophilic, PAS-positive spherules which are electron-dense and located within the cisternae of the endoplasmic reticulum (115,116). They appear to be immunoglobulins, perhaps L chains (117). Russell bodies also have been described in plasma cells from primary amyloid patients (111). Plasma cells containing numerous cytoplasmic vacuoles have been termed "Mott cells," "grape cells" and "morular cells;" these appear to be aggregates of Russell bodies. Other inclusions including crystals (118,119) and Auer-like bodies (120) occur rarely. Unusual cases in which plasma cells appear to be phagocytic (containing red cells, polymorphonuclear leukocytes, platelets and iron) have been reported (121,122).

Intracytoplasmic monoclonal immunoglobulin is demonstrable by the immunofluoresence (64,69,70) or immunoperoxidase (123,124) methods.

The number of peripheral blood B lymphocytes has been found to be reduced in myeloma patients but may rise after treatment (125-128). Some of the circulating B lymphocytes appear to bear the idiotypic determinants of the patient's myeloma protein (127-129); this finding of great potential significance. Recently, an in vitro assay which permits formation of colonies of human myeloma cells in soft agar has been developed (130).

An array of cytogenetic abnormalities in myeloma cells has been reported. Recent evidence indicates that genes on chromosome 14 may be involved in the regulation of lymphoid cell proliferation and lymphomas (131). An abnormal chromosome 14 with extra bands at the end of the long arm (14q+) has been observed in myeloma as well as lymphomas (132-134). This finding is not present in patients with myeloproliferative disorders and may represent a marker chromosome for lymphoid malignancy.

Additional studies. The recommended initial evaluation for a patient with known or suspected multiple myeloma is listed in Table 6. Quantification of serum M-protein usually can be determined from the SPE pattern (24). Reduction in the levels of normal serum immunoglobulins is generally present reflecting the fact that these patients typically manifest a poor antibody response following immunization (39,135-139). In addition to the studies discussed previously, serum calcium, BUN and/or creatinine, uric acid, and electrolyte values should be obtained (23,140). Some patients with myeloma and related plasma cell dyscrasias have a low anion gap (140-144); if present, this is a helpful diagnostic clue. Determination of the creatinine clearance should be done if the patient has BJP, amyloid or other renal disease. Bone roentgenograms should be obtained to identify lytic lesions. Osteosclerotic lesions are rare but do occur (97,145). Diffuse osteoporosis without lytic lesions is commonly seen; this finding is, of course, not diagnostic of myeloma (146-148). Because of the predominately lytic nature of bone destruction, bone scans are frequently negative in myeloma. Occasional patients present with apparently "solitary" intraosseous lytic defects which are found to be plasmacytomas at biopsy (see Case 3). Although evidence of other marrow involvement may not be demonstrable initially, typical "multiple" myeloma develops within 3 years in most instances (23,71). By contrast, extramedullary plasmacytomas may or may not be associated with identifiable M-proteins and progressive disease (72-90). Other studies listed in Table 6 as "Contingent Procedures" should be obtained, if indicated.

The dangers of intravenous pyelography (IVP) in myeloma patients with Bence Jones proteinuria has been documented repeatedly (23,140). This radiographic examination is most likely to be obtained in the patient with undiagnosed myeloma who presents with renal failure of "unknown" etiology (see Case 1). It is just this circumstance in which the identification and quantification of proteinuria becomes critical, since dehydration prior to IVP can lead to irreversible renal failure in patients with Bence Jones proteinuria. If an IVP is required in such a patient, he should not be dehydrated prior to the procedure.

TABLE 6. Recommendations for the Diagnostic Evaluation of Patients with Plasma Cell Dyscrasias

Mandatory Procedures

- History
- Physical examination
- Laboratory tests
  - CBC and platelet count
  - Serum protein electrophoresis and immunoelectrophoresis
  - Serum calcium, BUN/creatinine, uric acid & electrolytes
  - Urine protein screen (SSA/TSA)
  - Quantitative 24 hr urinary protein excretion
  - Urine protein electrophoresis and immunoelectrophoresis
- Radiographic examinations
  - Chest
  - Bone survey
- Bone marrow aspirate/biopsy*

Contingent Procedures

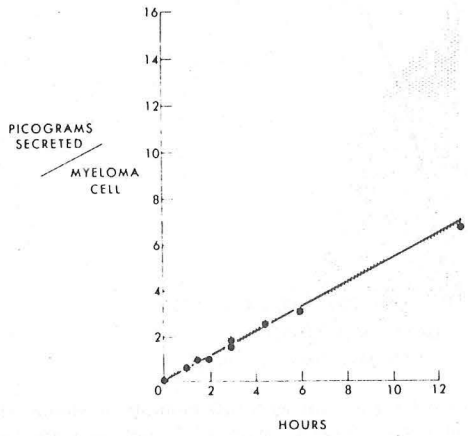
- ESR
- Quantitative serum immunoglobulins
- Creatinine clearance
- Coagulation studies, bleeding time
- Rectal biopsy for amyloid**
- Serum viscosity determination
- Serum cryoglobulin determination
- Rheumatoid factor titer
- Cold agglutinin titer
- Other tissue biopsies: Lymph node, small bowel, etc.

* Whenever possible, both aspirate and biopsy should be obtained.

** Tissue should be examined by Congo red staining under polarized light and by electron microscopy.

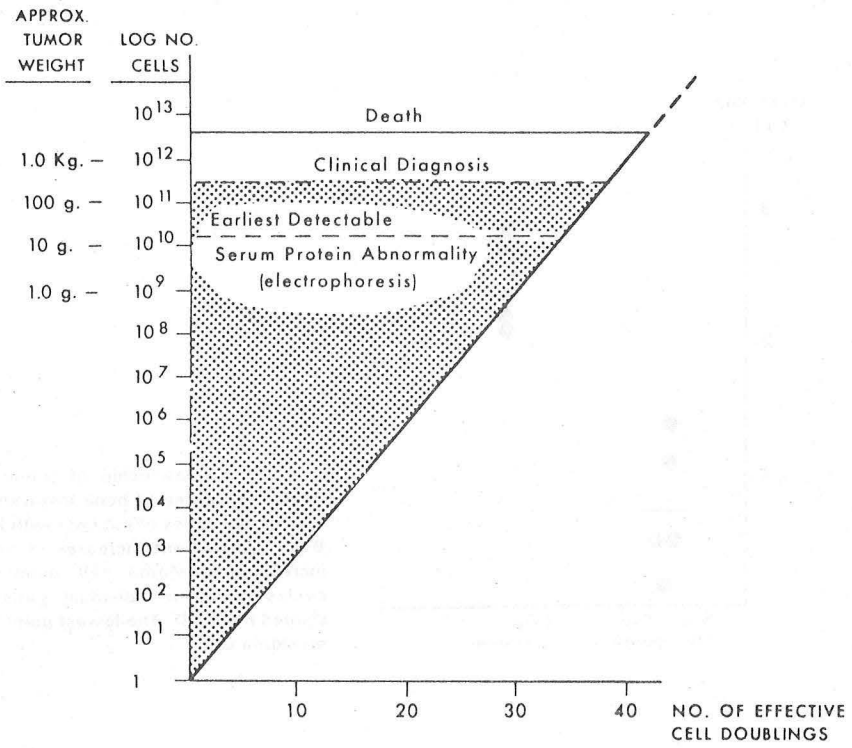
On the basis of cell kinetic studies, Salmon has confirmed the fact that the amount of M-protein reflects the magnitude of the tumor cell burden in myeloma patients (Fig 7A-D) (149).

Fig. 7A



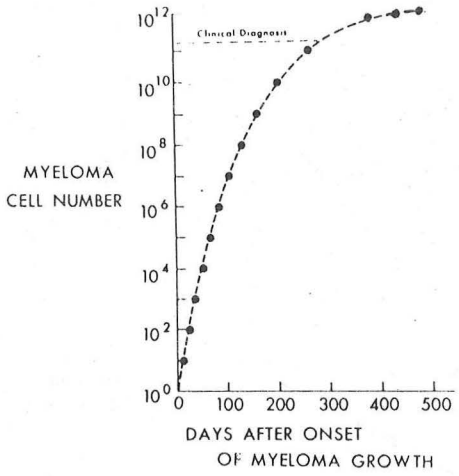
A typical secretion rate experiment with multiple points. This patient's myeloma cells had an average in vitro secretory rate of 12.9 pg per myeloma cell/day. The intracellular pool size of immunoglobulin, which is not shown in this illustration, did not change in size during the culture period. The shaded area encompasses the cellular secretory rates of 95% of the myeloma patients studied.

Fig. 7B



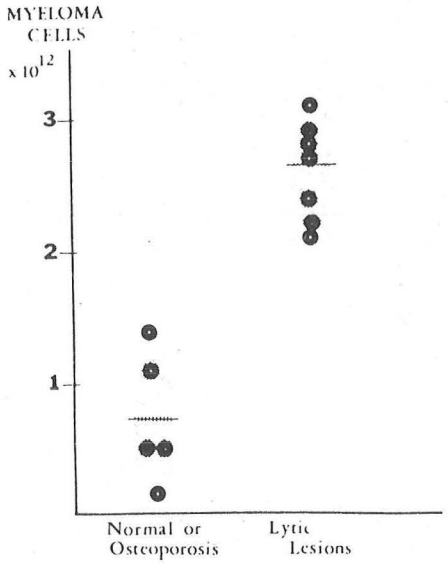
Relation of tumor weight and cell number to the number of effective cell doublings from the initiation of a malignant monoclone. It should be emphasized that time is not shown on the abscissa of this graph, because the tumor cell doubling time is not constant. The figure is designed to show the "iceberg" of preclinical doublings that go on prior to potential detection of an M-component on serum electrophoresis. Clinical diagnosis is generally about one or more logs above that point.

Fig. 7C



Gompertzian curve of tumor growth for a patient with IgG multiple myeloma. The data points are computer-generated and placed at 1 log intervals, up to 10^{12} cells, and are based on back extrapolation from tumor cell number determinations in the clinical phase of illness. In this patient, the preclinical phase appears to be less than 1 yr in duration.

Fig. 7D



Relationship of tumor cell number to clinical degree of bone involvement in a representative series of patients with IgG myeloma. Bone involvement increases in frequency with increasing myeloma cell number. The dark circles represent individual patients, and the shaded bar 1 SD. The lowest point is 0.3 x 10^{12} myeloma cells.

Thus the serum and/or urine M-components serve as markers which are useful not only in diagnosis but also in determination of the extent of disease. The initial staging criteria for myeloma patients which have been derived from such kinetic studies (100) is shown in Table 7.

Table 7. Myeloma Staging System

Stage I: Low cell mass (< 0.6 X $10^{12}/m^2$ myeloma cells)*

All of the following:

- Hemoglobin > 10 g/100 ml
- Serum calcium normal (≤ 12 mg/100 ml)
- On roentgenogram, normal bone structure or solitary bone plasmacytoma only
- Low M component production rates
  - IgG < 5 gm/100 ml
  - IgA < 3 gm/100 ml
  - Bence Jones proteinuria < 4 g/24 hr

Stage II: Intermediate cell mass (0.6-1.2 X $10^{12}/m^2$ myeloma cells)
Fitting neither Stage I nor Stage III

Stage III: High cell mass (> 1.2 X $10^{12}/m^2$ myeloma cells)

One or more of the following:

- Hemoglobin < 8.5 g/100 ml
- Serum calcium > 12 mg/100 ml
- Advanced lytic bone lesions
- High M component production rates
  - IgG > 7g/100 ml
  - IgA > 5g/100 ml
  - Bence Jones proteinuria > 12 g/24 hr

Subclassification:

A = relatively normal renal function (serum creatinine < 2.0 mg/100 ml)
B = abnormal renal function (serum creatinine ≥ 2.0 mg/100 ml)

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* 10^{12} cells ∿ 1 kg; m = square meter of body surface area.
Modified from Durie & Salmon (100)

VI. MYELOMA AND AMYLOID

It has long been known that 10-15% of patients with typical multiple myeloma have amyloid demonstrable in various organs at autopsy. More recently, it has become clear that most patients presenting with the manifestations of "primary" systemic amyloidosis of the non-hereditary type have a monoclonal immunoglobulin abnormality identifiable in serum and/or urine. Amyloid deposition in these individuals tends to be distributed in the heart, tongue, gastrointestinal tract, skin, ligaments, and peripheral nerves (150). However, involvement of liver, kidneys, spleen, and adrenals -- a distribution more characteristic of "secondary" amyloidosis may also occur. Because of this overlap in distribution of amyloid, differentiation into "primary" and "secondary" types on the basis of organ involvement is not helpful in the individual patient.

The principal reason for retaining the "primary" and "secondary" nomenclature rests on the demonstration of the chemically distinct nature of amyloid fibrils found in patients in whom a recognizable, coexisting, chronic infectious or inflammatory disease is ("secondary") or is not ("primary") present. Although amyloid fibrils from various sources share the same physical properties as delineated by Congo red staining under polarized light, electron microscopy and x-ray diffraction patterns, chemical studies have revealed two major types of amyloid fibril proteins (Table 8).

In patients with non-familial "primary" systemic amyloidosis or plasma cell dyscrasia-associated amyloidosis, the major constituent of the isolated amyloid fibril proteins consists of intact monoclonal immunoglobulin light chains and/or fragments from their N-terminal (variable) region (151-153). Therefore, the amyloid in these patients appears to consist of extracellular deposits of intact or fragmented Bence Jones proteins. In our experience, approximately 80% of patients presenting with "primary" (i.e., without evidence of coexisting chronic infectious or inflammatory disease) systemic amyloidosis have identifiable M-protein abnormalities in serum and/or urine. The most commonly observed M-protein abnormality consists of Bence Jones protein exclusively (23,154). Thus accurate characterization of urinary proteins is critically important in this group of patients. Approximately 15% of Bence Jones protein appear to be "amyloidogenic;" i.e., they have the property of precipitating as fibrillar material resembling amyloid following in vitro proteolytic digestion. This amyloidogenic property is more commonly observed with λ than with κ monoclonal light chains.

Our previous study of 35 patients with light chain myeloma (23) included 7 subjects who presented with primary systemic amyloidosis (see Case 4). The carpal-tunnel syndrome, macroglossia, congestive heart failure, arthralgias, peripheral neuropathy and gastrointestinal bleeding were findings confined to the amyloid group. By contrast, patients without evidence of amyloid presented with the typical

TABLE 8. Characterization of Human Amyloid Fibrils

Physical properties (common to all forms of amyloid)
Polarized light: green birefringence with Congo red
EM appearance: 70 to 100 Å nonbranching fibrils
X-ray diffraction pattern: β-pleated sheet conformation
Chemical studies (at least two distinct types of amyloid proteins)
Intact monoclonal immunoglobulin light chains and/or fragments from N-terminal (variable) region
Patients with nonfamilial primary systemic or plasma cell dyscrasia-associated amyloidosis
Approximately 15% of Bence Jones proteins apparently "amyloidogenic" ($\lambda > \kappa$)
Protein AA (also known as AS or ASF) - not derived from L chains
Patients with secondary amyloidosis (rheumatoid arthritis, bronchiectasis, tuberculosis, Hodgkin's and familial Mediterranean fever)
Mol wt ≈ 9,000-12,000 daltons
No relationahip to any known immunoglobulin fragment
Origin obscure but appears related to minor component in normal serum
Additional types of amyloid proteins reported

Revised from (5)

symptoms of myeloma (skeletal pain, renal failure etc). Although we could not prove that all patients in this latter group had no tissue amyloid, we failed to obtain evidence for it at autopsy or on various biopsies in 16 of these 28 individuals. Clinical and laboratory findings in the amyloid and "nonamyloid" LCD patients are shown in Table 9.

Table 9. **Comparison of Clinical and Laboratory Features in Patients With and Without Amyloid**

Parameter	With Amyloid	Without Amyloid	
Patients (no.)	7	28	
Light chain class	3κ, 4λ	13κ, 15λ	
Mean age (yr)	56	60	
Mean hemoglobin (g/100 ml)	11.7	11.4	
Mean blood urea nitrogen (mg/100 ml)	28	40	
Mean serum creatinine (mg/100 ml)	3.3	3.3	
Mean serum calcium (mg/100 ml)	9.7	11.1	
Mean serum uric acid (mg/100 ml)	8.1	8.4	
Mean serum albumin (g/100 ml)	3.0	3.9	$p < 0.01$
Mean serum IgG (mg/ml)	5.0	6.8	
Bence Jones proteinemia	6/7	22/28	
Lytic bone lesions (%)	1/7	21/28	$p < 0.025$
Marrow plasma cells (%)	50	54	
Mean 24 hour proteinuria (g)	3.80	3.05	
Median survival (mo)	7	19	$p < 0.001$

(23)

The recent insights into the chemical nature of amyloid fibrils have clinical implications which are pertinent to our study. The amyloid patients presented with complaints directly relating to tissue deposition of amyloid, whereas the other LCD patients exhibited the usual symptoms and signs of myeloma. Yet the monoclonal light chain abnormality and degree of evident plasma cell proliferation were similar in both groups. These considerations emphasize that the distinction between "primary amyloidosis associated with plasmacytic dyscrasia" and "myeloma-associated amyloidosis" is vague, particularly when the M-protein disturbance involves overproduction of Bence Jones protein exclusively. The experimental studies relating BJP and amyloid may explain the rather high incidence (20 per cent)

of amyloidosis which we observed. Amyloid has been identified only rarely in the remainder of our myeloma population, a finding similar to that of Hobbs (62). Thus accurate appraisal of the incidence of amyloidosis in multiple myeloma is largely dependent on the LCD subgroup. The data are consistent with the hypothesis that LCD patients who synthesize and secrete Bence Jones proteins possessing "amyloidogenic" properties tend to have an illness dominated by the features of primary amyloidosis instead of the usual manifestations noted in other myeloma patients. The resulting clinical picture would be, therefore, more dependent on the molecular structure of the individual Bence Jones protein produced than on any intrinsic difference between primary amyloidosis and multiple myeloma. Such a hypothesis does not dictate that every patient producing "amyloidogenic" light chains need necessarily develop clinical amyloidosis; some clearly do not (151,153) suggesting that additional factors play a role in the tissue deposition of amyloid fibrils (155).

Skeletal destruction was rare in the amyloid group. In fact only 1 of 7 patients had an osteolytic lesion. This rarity may be due to an earlier presentation of patients because of symptoms referable to the amyloid deposition. Cell kinetic data in IgG myeloma support such a concept since patients with more than 2 X 10^{12} "myeloma" cells generally have osteolytic lesions whereas such lesions are usually absent when the tumor cell burden is less than 1 X 10^{12} cells (Fig D). This hypothesis has not been tested by cell kinetic studies in LCD.

In contrast to primary amyloidosis, patients with amyloidosis "secondary" to rheumatoid arthritis, bronchiectasis, tuberculosis, Hodgkin's disease, and familial Mediterranean fever (FMF), have as the major constituent in their amyloid fibrils a protein (called Protein AA, AS or ASF) which is not derived from immunoglobulin L chains (156). The molecular weight of this protein is in the range of 9-12,000 daltons and it bears no identifiable relationship to any known immunoglobulin chain or fragment (Table 8). Its origin is obscure but it appears to be related to some minor component present in normal serum (157). Amyloid AA has been found in fibroblasts (158), plasma cells and Kupffer cells (159), and polymorphonuclear leukocytes (160).

Additional chemical types of amyloid appear likely, particularly those noted in association with tumors of endocrine glands (e.g., medullary thyroid carcinoma and islet-cell tumors of the pancreas) (161). Another chemically distinct type of amyloid (protein A_{SCA}) has been described recently from individuals with senile cardiac amyloidosis (162). Thus a rational classification of amyloid is (at last) beginning to emerge (Table 10).

Table 10. CLASSIFICATION OF AMYLOIDOSIS ACCORDING TO MAJOR PROTEIN CONSTITUENT OF FIBRILS

Type	Protein Component
1. Primary systemic amyloid (non-hereditary)	BJP
2. Amyloid associated with plasma cell dyscrasias	BJP
3. Secondary systemic amyloid	AA
4. Familial amyloid (FMF)	AA
5. Senile amyloid (cardiac)	A_{SCA}
6. Amyloid associated with endocrine tumors (MCT)	Peptide hormone
7. Localized amyloid	?

Symptoms and signs. Presenting manifestations are variable and depend on the organ or system which is predominantly involved. Thus, intractable low-output cardiac failure with or without conduction defects and arrhythmias, macroglossia, gastrointestinal bleeding or diarrhea, carpal-tunnel syndrome, arthralgias associated with periarticular thickening, autonomic or peripheral neuropathy, skin plaques and purpura, hepatosplenomegaly or massive proteinuria may be seen (163).

Diagnosis. Amyloidosis can be diagnosed only by biopsy (164). The finding of fibrillar material in urinary sediments is nonspecific and this method should not be employed to establish the diagnosis (165). Tissue should be stained with Congo red and examined under polarized light for presence of the characteristic yellow-green birefringence. The typical fibrillar structure is well demonstrated by electron microscopy. Biopsy of rectal mucosa is the safest and most convenient screening procedure (163). In any patient found to have "primary" amyloid, a careful search should be made for the presence of a homogeneous immunoglobulin or light chain in both serum and concentrated urine (23). Bence Jones proteinuria without an accompanying serum M-spike is the abnormality most frequently encountered.

The bone marrow should be examined for evidence of plasmacytosis as well as amyloid. Evidence of "functional" hyposplenism (consisting of the triad of findings of abnormal red cell forms with Howell-Jolly bodies on peripheral blood smear, reduced or absent splenic uptake following injection of ^{99m}Tc-sulfur colloid, and splenomegaly) has been documented in approximately 15% of our amyloid patients in Dallas.

An approach to the classification of amyloidosis on the basis of clinical findings is shown in Table 11.

Table 11. CLINICAL CLASSIFICATION OF AMYLOIDOSIS

1. Primary Systemic (nonhereditary)
   - A. Immunoglobulin-derived
     - i) M-component (usually Bence Jones protein) demonstrable in urine and/or serum
     - ii) Overt myeloma may or may not be present
   - B. Non-immunoglobulin-derived
     - i) No demonstrable Bence Jones protein
     - ii) Uncommon
2. Secondary Systemic
   - A. Chronic disease association: TB, bronchiectasis, osteomyelitis, rheum. arthritis, leprosy, paraplegia, inflammatory bowel disease, Hodgkin's, renal cell carcinoma, etc.
   - B. Most appear to be of non-immunoglobulin origin (no demonstrable Bence Jones protein)
3. Heredofamilial
4. Senile
5. Localized
   - A. Amyloid "tumors" - esp. respiratory and urinary tracts
   - B. Neoplasms with amyloid stroma - endocrine tumors

VII. OCCULT (ASYMPTOMATIC) PLASMA CELL DYSCRASIAS

Plasma cell dyscrasias of unknown significance (PCDUS). As noted, the advent of SPE as a routine diagnostic test during the past decade has led to the relatively common finding of a homogeneous

immunoglobulin in serum of patients with a wide variety of "non-myelomatous" disorders (23,166-168). These fortuitously discovered M-proteins have been documented in patients with chronic infectious and inflammatory diseases, non-reticular neoplasms, storage diaseases, and many other disorders. Most of these individuals do not have additional evidence of multiple myeloma or other "overt" plasma cell dyscrasias at the time these serum M-spikes are found. However, it appears that < 5% of such instances occur in patients with "presymptomatic" myeloma, in which the serum M-protein abnormality is discovered because a SPE was obtained (see Case 5). Unfortunately, no reliable method is presently available to distinguish this small group of "pre-myeloma" individuals from those with stable, non-progressive plasma cell dyscrasias (18,169). Moreover, evolution to full-blown myeloma may take as long as twenty years to occur. With the recognition that at least some (? most) monoclonal immunoglobulins in humans and experimental animals appear to be true antibodies (Section IX), it seems likely that many M-proteins in patients with PCDUS may, in fact, represent monoclonal antibody responses. This conclusion is also supported by the finding of serum M-proteins in healthy individuals; in this case, the incidence is age-related. Thus 1% of normal persons age 25 and 3% of individuals age 70 have such monoclonal immunoglobulins detectable in their serum. In the majority of cases of PCDUS, the immunoglobulin abnormality present is IgG. That this is a common finding is illustrated by the fact that approximately 30% of patients having serum monoclonal IgG components identified in our laboratory have been those in whom PCDUS was present (Table 5). IgA and IgM M-components may be found in this group of patients but are less common.

It is important to evaluate the patient having a fortuitously discovered serum M-spike for other evidence of myeloma. The criteria for the diagnosis of myeloma (vide supra) must be borne in mind in this regard. Features which we have found helpful in differentiating patients with myeloma from those with PCDUS are shown in Table 12.

By definition, patients with an apparently nonprogressive or stable plasma cell dyscrasia (PCDUS) do not have sheets or clusters of marrow plasma cells, Bence Jones proteinuria or lytic bone lesions. Similarly, such individuals would not be expected to have amyloidosis or unexplained renal failure. Moreover, since the quantity of the M-component bears a direct relationship to the tumor cell burden, patients with nonprogressive plasma cell dyscrasias generally tend to have lower serum M-spikes than is true in myeloma patients. In this regard, it may be helpful to note that the average patient with IgG myeloma has a 4.3 gm/dl serum M-spike, while the average serum M component in patients with IgA myeloma is approximately 2.8 gm/dl (62). The most characteristic feature of patients with these apparently "benign" plasma cell tumors is the absence of a rise in the serum M-component on serial serum protein electrophoresis analyses. We generally repeat the SPE at 4-6 month intervals. Only in the event of a significant increase in the quantity of serum M-protein (greater than 0.5 gm/dl) do we repeat the diagnostic evaluation for myeloma (Table 6).

Table 12. FINDINGS USEFUL IN DISTINGUISHING OVERT FROM OCCULT PLASMA CELL DYSCRASIAS (PCD)

Favor Overt PCD:

- Marrow plasma cells in sheets or clusters
- Bence Jones proteinuria (> 300 mg/24 hr)
- Lytic bone lesions
- Systemic amyloidosis
- Rising serum M-spike
- Progressive unexplained renal failure
- Recurrent bacterial infections
- Reduced levels of normal serum immunoglobulins

Favor Occult PCD:

- Minor marrow plasmacytosis (no sheets or clusters)
- Absence of Bence Jones proteinuria
- Absence of osteolytic lesions
- Absence of systemic amyloidosis
- Stable, small serum M-spike (< 2.5 gm%), esp. if IgG
- Normal levels of serum immunoglobulins
- Age > 70 yr (3% incidence)

Patients with PCDUS should be distinguished from the myeloma population, since the former should not receive cytotoxic chemotherapy, while most patients with overt disease require such treatment. Even in those few PCDUS patients with pre-myeloma, the evolution to clinically significant disease may require many years to occur, as noted. Because of the uncommon but well-documented development of acute granulocytic and monocytic leukemias in treated myeloma patients who have responded to therapy with alkylating agents (170-172), patients with PCDUS should not be treated until there is unequivocal evidence of malignancy.

VIII. "PARANEOPLASTIC" MANIFESTATIONS OF MYELOMA AND OTHER PLASMA CELL DYSCRASIAS

In addition to amyloidosis, an array of other syndromes may be associated with myeloma and related plasma cell disorders (Tables 13-17).

Table 13. TENTATIVE EXPLANATIONS FOR SPECIFIC "PARANEOPLASTIC" MANIFESTATIONS OF PLASMA CELL DYSCRASIAS*

A. Disorders that Result from Antibody Activity of Certain M-Components	
Mixed cryoglobulinemia (16,174-176)	usually monoclonal IgM with anti-IgG activity, occasionally IgM anti-IgA, IgA anti-IgG, or IgG anti-IgG, "rheumatoid factors"
Cold agglutinin disease (177-180)	anti-I antibody, directed towards red cell membrane - usually IgM, rarely IgA
Bleeding syndromes associated with circulating anticoagulants or platelet functional defects (181-184)	complex (? immune) of M-protein with various coagulation factors or platelets
Hyperlipidemia (185-190)	anti-lipoprotein antibody - IgA or IgG

Table 13 (continued)

B. Disorders that result from Effects of Certain Physicochemical Properties of M-Components

Hyperviscosity syndrome (191-201)	IgM M-components with high intrinsic viscosity; IgA or IgG M-components with tendency to spontaneous aggregation
"Myeloma kidney" (23,202-211)	free light chains or light-chain dimers synthesized in tremendous excess and filtered by kidney, and resulting in renal injury (tubular atrophy)
Renal tubular acidosis (± Fanconi syndrome) (23,118,212-217)	presumably an effect of certain free light chains or light-chain dimers (uncertain)
Amyloidosis (23,102,150-165)	synthesis and secretion of variable fragment of light chains with high propensity for deposition in tissues (Bence Jones dimer a primitive antibody?)
Cryoglobulinemia (175,218,219)	M-component with narrow thermal amplitude
Multiple organ dysfunction (220)	Systemic L chain deposition (not amyloid)
Motor neuropathy (221)	LCD (λ); ? mechanism
Systemic capillary leak (222)	IgG; ? mechanism
Decreased chemotaxis (223)	IgA ? steric hindrance of cell receptors

C. Disorders that May Result from Release of Other Products of R-E cells or B cell monoclones

Antibody deficiency syndrome (224-227)	secretion of "chalone," which halts formation or proliferation of B lymphocytes of all immunologic specificities and immunoglobulin classes (may involve monocyte-macrophage suppressor cells)
(6)	secretion of large amount of IgG M-component, which results in hypercatabolism of all IgG; no effect on other immunoglobulin classes
Hypercalcemia (228-230)	release of calcium-mobilizing substance (OAF) by plasma cells

* Revised and expanded from (173)

TABLE 14. SIGNS AND SYMPTOMS OF THE HYPERVISCOSITY SYNDROME

Ocular	Disturbance in vision to complete loss of vision; Distension and tortuosity of retinal veins "string-of-sausage" appearance
Hematologic	Oozing of blood from oral mucous membranes Bleeding from nose, urinary and gastro-intestinal tract Prolonged bleeding at sites of minor surgical procedures Anemia
Neurologic	Headache, dizziness, vertigo, nystagmus postural hypotension Somnolence, stupor, and coma Generalized seizures, EEG changes Hearing loss
Cardiovascular	Congestive heart failure Expanded plasma volume
Renal	Glomerular deposits attributable to HVS? Diminished concentrating and diluting ability attributable to HVS?
Subjective	Weakness, fatigue, anorexia

From (196)

TABLE 15. HEMOSTATIC ABNORMALITIES ASSOCIATED WITH DYSPROTEINEMIAS

I. Hemorrhagic Abnormalities

A. Abnormalities of Platelets

1. Thrombocytopenia
2. Impaired Function

B. Abnormalities of Plasma Coagulation Factors

1. Inhibitors of Coagulation

a. Fibrin monomer aggregation
b. Factor VIII
c. nonspecific - usually detected by thromboplastin generation test
d. other coagulation factors
e. Factor X deficiency due to in vivo inactivation

2. Depression of Clotting Factors

C. Hyperviscosity Syndrome

D. Miscellaneous

II. Thrombotic Abnormalities

From (183)

TABLE 16. SOME DISORDERS ASSOCIATED WITH CRYOGLOBULINEMIA

Myeloma and macroglobulinemia
Diffuse lymphoma and chronic lymphocytic leukemia
Connective tissue diseases
  Systemic lupus erythematosus
  Polyarterities nodosa
  Sjögren's syndrome
  Rheumatoid arthritis
  Juvenile rheumatoid arthritis
  Ankylosing spondylitis
  Lyme arthritis
Renal disease (glomerulonephritis, nephrotic syndrome, renal tubular acidosis)
Cirrhosis & chronic active hepatitis
Sarcoidosis
Purpura-arthralgia syndrome
Infections
  Infectious mononucleosis
  Bacterial endocarditis
  Leprosy
  Cytomegalovirus
  Syphilis
  Hepatitis B
  Malaria
Status post-intestinal bypass surgery for obesity

From (231)

TABLE 17. MANIFESTATIONS OF CRYOGLOBULINEMIA

Weakness
Purpura (dependent)
Arthralgias
Raynaud's phenomenon
Acrocyanosis (occ. peripheral gangrene)
Livido reticularis
Cold urticaria
Cutaneous vasculitis with ulceration
Visual disturbances and retinal hemorrhages
Mucosal bleeding tendency
Cerebral thrombosis
Lymphadenopathy
Hepatosplenomegaly
Renal disease (proliferative glomerulonephritis, nephrotic syndrome, renal tubular acidosis)
None

From (231)

IX. ARE MYELOMA PROTEINS ANTIBODIES?

In humans and animals, the usual antibody response to injected antigen is heterogeneous. This heterogeneity is reflected at various levels (class, subclass, L chain type, electrophoretic mobility, affinity constants, etc). During the past decade, however, evidence has accumulated that antibodies to certain antigens may be much less heterogeneous than previously thought. Indeed it appears that monoclonal antibodies may arise during the course of a normal immune response (2,16,232). Krause, Haber and their coworkers have demonstrated that high concentrations of monoclonal antibodies appear in the sera of occasional rabbits immunized with streptococcal and pneumococcal polysaccharides (Fig 8, Table 18). There is no evidence of a plasma cell dyscrasia in these animals and the serum antibody levels to the immunizing antigen may rise to concentrations of 30-60 mg/ml; moreover, they decrease with time unless the rabbits are further challenged with antigen (Fig 8).

Monoclonal antibodies (or antibodies with restricted heterogeneity) also have been documented in humans without evidence of plasma cell dyscrasias. Thus most antibodies to Factor VIII (found in hemophiliacs, postpartum women and elderly patients) are of the IgG4 subclass; many antibodies to polysaccharide antigens belong to the IgG2 subclass; and the antiplatelet antibodies occurring in patients with idiopathic immunologic thrombocytopenic purpura are predominately of the IgG3 subclass (21).

Transient plasma cell dyscrasias have been documented in humans (233) (Table 1) and, as noted, stable non-progressive plasma cell dyscrasias are frequently seen in patients with a variety of other disorders. Although defined antigenic specificities have rarely been documented in these populations of individuals, some of them may represent monoclonal antibody responses to unrecognized antigens.

Functional antibody activity to human and murine myeloma proteins was first demonstrated unequivocally in 1967 (234-237). Since then, a number of other examples have been demonstrated in patients with myeloma or macroglobulinemia (Table 19) and in mice with induced plasma cell tumors (Table 20).

Although the possibility that myeloma proteins might represent the products of a directed immune response has been raised on clinical grounds alone (246-252), the number of patients with documented antigen-binding M-proteins in whom the antigen appeared meaningful has been sparse. Two examples are noteworthy: one patient with a history of recurrent episodes of rheumatic fever who developed myeloma with an IgG M-protein having antistreptolysin activity (219) and another patient who had received 2 injections of unpurified horse serum 6 years apart who years later developed myeloma with an IgG M-component having specificity for horse α-2 macroglobulin (241).

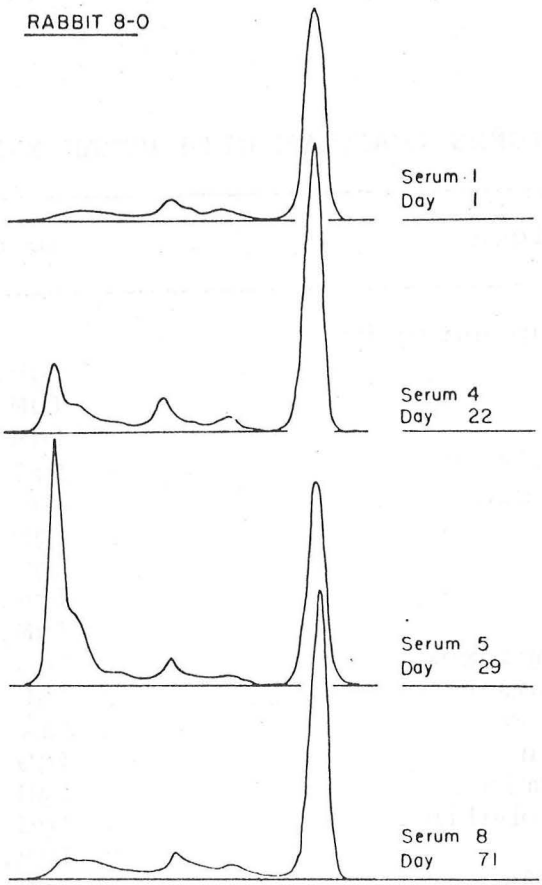

Fig. 8. Tracings of the densitometric scans of the zone electrophoretic patterns for sera collected before, during, and after immunization of the rabbit. (232)

Table 18.

Characteristics Indicative of Antibody Uniformity

Monodisperse by zone electrophoresis
Individual antigenic specificity
Single class and single subgroup
Selective absence of allotypic markers
Homogeneous binding characteristics
Monodisperse light chains by disc electrophoresis
Single light-chain type
Amino acid sequence analysis

(232)

Table 19. ANTIGENS REACTIVE WITH HUMAN MYELOMA PROTEINS

Antigen	Ig class
Blood group antigens	
I, i	IgM, IgA
Sp_1	IgM
A_1	IgM
Streptolysin O	IgG
Staphylolysin	IgG
Klebsiella	IgM
Brucella	IgG
Rubella	IgG
IgG	IgM,IgG,IgA
Immune complexes	IgM
Fibrin monomer	IgG
Lipoproteins	IgA,IgG
Transferrin	IgG
Serum albumin	IgM
α_2-Macroglobulin	IgG
Dnp	IgM,IgG,IgA
Cardiolipids	IgM
Phosphorylcholine	IgM
Riboflavin	IgG

Antigens included are those for which evidence of specificity is strongest. Revised from (2). Also see refs 16,174,219, 232,234-236,238-243.

Table 20. MOUSE MYELOMA PROTEINS WITH ANTIBODY ACTIVITY AGAINST ANTIGENS IN THE ENVIRONMENT OF THE MOUSE

Antigenic activity	Suspected natural antigenic source
Mima antigen	*Mima polymorpha*
Phosphorylcholine	*Lactobacillus*-A
	Trichoderma
β(1→6)-D-Galactan	Wheat
	Hardwood beeding
α(1→3)Dextran	Various possible bacterial sources
Fructosan	*Bacillus circulans*
α-Methyl-D-galactoside	*Proteus mirabilis* sp-2
α-Methyl-D-mannoside	*Proteus mirabilis* sp-2
Common trypsin-sensitive *Salmonella* antigen	*Pasteurella pneumotropica*
Pronase-sensitive antigen in wheat extract	Wheat extract

The known antigenic activity and suspected natural antigenic source are given. For some antigens, e.g., phosphorylcholine, α(1→3)dextran, and β(1→6)-D-galactan, a number of myeloma proteins with the same specific antibody activity have been identified. From (2). Also see refs 237,238,240,244,245.

We have already discussed the data relating to the structural similarity between M-proteins and typical antibody immunoglobulin molecules. Though the former have often been referred to as "paraproteins," detailed investigation has failed to generate convincing evidence of abnormality. On the contrary, most available evidence is consistent with the proposition that monoclonal immunoglobulins are normal products of a restricted population, or clone, of cells that for unclear reasons, has undergone intense proliferation. Antigen-binding activity of myeloma proteins is chemically indistinguishable from that observed with conventionally induced antibodies and has been found in all three major classes of immunoglobulins (IgG, IgM and IgA). The determinants thus far identified include representatives from each of the classical types of antigen molecules: proteins, polysaccharides and haptens. Protein and polysaccharide antigens may represent meaningful responses since they are constituents of autoantigens or other substances with which a host is likely to come in contact. Such findings suggest that an expanded clone of cells is more likely to undergo neoplastic transformation or that certain clones may be more susceptible to such transformation. While normal clones are antigen-regulated and pathologic ones presumably not, antigen can nonetheless be involved in the developmental history of the abnormal clone up to the time at which the neoplastic event occurred. The virtual inability to induce myeloma in the murine system when germ-free mice are employed supports the role of an expanded clone as a necessary prerequisite to the development of a malignant plasma cell dyscrasia (253).

The significance of demonstrated binding activity for haptens (some of which do not occur naturally) is less clear. Although the history of immunochemistry abounds with studies of immunological specificity that demonstrate that combination of antibody with antigen is not only specific but is also restricted to the inducing antigen or structurally-related similar compounds (cross-reactivity), some investigators have recently raised the possibility that antibody combining sites might be multispecific (polyfunctional) (254-257). This point remains highly controversial. Moreover, the number of myeloma proteins examined for antibody activity is limited by available assays for a rather small number of antigens. Finally, detection of binding activity is more difficult for homogeneous immunoglobulins than for usual heterogeneous antibodies.

Thus, some (? all) myeloma proteins are antibodies but the biological significance of this interesting finding in the pathogenesis of myeloma awaits further investigation.

X. PROGNOSIS AND THERAPY

Myeloma is a progressive disorder although the rate of progression varies considerably among different patients. Optimal management improves both the quality and duration of life. Survival is related to the time of diagnosis, adequacy of supportive measures, and response to chemotherapy. High levels of M-protein in serum or urine, diffuse bone lesions, hypercalcemia, severe anemia or pancytopenia, and renal failure are unfavorable signs.

Supportive Therapy. Maintenance of ambulation is vital. Analgesics and palliative doses of local raiotherapy (1000 to 1500 rads) to symptomatic bone lesions relieve pain in many patients. Pathologic fractures of long bones should be treated by surgical fixation. Adequate hydration also is essential. The physician must always be aware that dehydration prior to an IVP may precipitate acute oliguric renal failure in patients with Bence Jones proteinuria (23,140). By contrast, even patients with prolonged, heavy Bence Jones proteinuria may not manifest evidence of severe renal functional impairment if they are kept well hydrated (urine output > 1500 ml/24 hr). Some patients with renal failure have been maintained on chronic hemodialysis with good quality of life for extended periods (258). Saline diuresis, corticosteroids or mithramycin (259) are valuable for the temporary control of hypercalcemia. Allopurinol should be employed for the management of hyperuricemia. Appropriate antibiotics are indicated for active bacterial infections. Prophylactic gamma globulin and antibiotics may benefit the small subgroup of patients in whom recurrent bacterial infections are a major problem; it should be emphasized, however, that neither of these should be utilized as routine measures for all myeloma patients (260). Pneumococcal vaccine may be helpful but it should be borne in mind that these patients are poor antibody-formers and may not respond. Spinal cord compression due to extradural plasmacytomas should be treated with radiation therapy ± corticosteroids. If the neurologic deficit progresses or if myeloma has not been previously diagnosed, a laminectomy should be performed. The hyperviscosity syndrome (191-201) can be effectively treated by vigorous plasmapheresis. Cautious transfusion of packed red cells is indicated for severe anemia - the use of androgens has been disappointing. Calcium and fluoride supplements have been advocated for the treatment of myeloma bone disease but this approach has not achieved widespread acceptance (261).

Chemotherapy. The standard regimen remains melphalan and prednisone (262,263). Various schedules have been utilized but the intermittent high-dose method every 4 to 6 weeks has become the most widely accepted one. Objective improvement as documented by a 50% or greater reduction in serum or urine M-protein is obtained in the majority of patients (100,101). Survival in responding patients may be extended three to seven fold (median ∿ 2-1/2 yrs) (264). Melphalan also may be given in a daily oral fashion (264,265) and cyclophosphamide may be substituted for melphalan with approximately the same results (266-268). Leukopenia and thrombocytopenia develop with these agents, and dosage must be titrated in each patient.

A reduction in tumor mass in the range of 75 to 90% occurs in responding patients during the first 6 to 8 months of treatment. Thereafter, a "plateau phase" is reached and relapse appears to occur when a resistant subclone develops (269-272).

The labelling index (^{3}H-thymidine) of myeloma cells may be helpful in following patients on treatment:

Best responders: low L.I. which does not increase by end of induction chemotherapy

Poor responders (or rapid relapse): higher L.I. or > 2-fold rise in L.I. during induction

Non-responders: high tumor mass and high L.I.

Although chemotherapy with alkylating agents has usually been given indefinitely, this approach has been questioned because of the cell kinetics (i.e., the plateau phenomenon) and the increasing recognition that responding patients have an enhanced liklihood of developing acute leukemia (myelomonocytic, monocytic or erythroleukemia) (170-172). Thus cessation of Rx has been advocated by some investigators. The response rate to reinduction chemotherapy in such a circumstance varies widely and the issue of maintenance chemotherapy is unsettled at present.

Various multiple drug regimens are being assessed for non-responding or relapsing patients - agents employed include vincristine, adriamycin, BCNU, azathioprine, hexamethylmelamine and cis-platinum in addition to alkylating agents (271,273-278). The recent development of a soft agar colony forming assay for human myeloma stem cells offers a promising new approach for the in vitro prediction of drug sensitivity for individual patients (130,279). Initial results with various chemotherapeutic agents show a strong correlation between in vitro and in vivo sensitivity or resistance.

The outlook for patients with nonhereditary primary systemic amyloidosis is poor, median survival after diagnosis ranging from 7 to 13 months. In those patients with demonstrable BJP, it seems rational to suppress L chain production by plasma cells with cytotoxic agents so that further deposition in tissues is diminished (23). Although encouraging results have been reported in a few patients with primary renal amyloidosis, such myeloma-type therapy has not been extensively evaluated. A recent report suggests that about 50% of patients with primary systemic amyloidosis treated with alkylating agents improve but that survival is not prolonged when compared to untreated controls (280). Since amyloid is known to arise from several non-immunoglobulin proteins (Section VI) and its deposition in experimental animals may be enhanced by immunosuppressive agents (23), cytotoxic chemotherapy is not recommended for patients without BJP.

Evidence from both experimental animals and patients with familial Mediterranean fever suggest that colchicine may inhibit tissue

deposition of amyloid or perhaps even reverse it (281,282). Although the mechanism of action is unknown, it is probably worthwhile to consider the use of colchicine in amyloid patients.

Native amyloid fibrils are insoluble in physiological media and are relatively resistant to chemical, physical and proteolytic agents. Once deposited in tissues, their extracellular location makes them inaccessible. Despite these discouraging facts, the observations in patients with secondary amyloidosis indicate that tissue deposits can be mobilized if the inciting stimulus to their production is removed. Hopefully, further elucidation of the mechanisms responsible for resorption in various sites will lead to effective therapy for patients with the primary systemic type.

XI. UNRESOLVED ISSUES AND FUTURE DIRECTIONS

1) What is the frequency of surface Ig receptors on human myeloma cells? What is the status of B lymphocytes? Does plasma cell RNA "convert" normal B cells into myeloma protein-secreting plasma cells? Are myeloma proteins tumor-specific antigens in humans? Would idiotypic antibodies made to a patient's myeloma protein have any therapeutic efficacy (126-129, 283-288)?

2) What is the natural history of abnormal Ig-producing clones? What is the cellular event which transforms the hyperplastic immune response of an expanded (i.e. antigen-stimulated) clone into an autonomous neoplastic clone (289,290)?

3) What is the biological role of myeloma antibodies? Are they accidents or meaningful? What are the antigens to which they are directed? Are antibodies multispecific (polyfunctional)? Can somatic cell hybridization technics be utilized to improve our ability to detect antigen-binding myeloma proteins (Section IX) (291-294)?

4) Are the M-proteins in patients with PCDUS antibodies? What are the critical factors determining whether an antibody response is homogeneous or heterogeneous (Section IX) (290,291)?

5) What is the role of T lymphocytes and macrophages? What is the molecular mechanism of normal Ig suppression (cell contact, humoral factor)? What is the status of cellular immunity in myeloma patients (224-227,288)?

6) What is the mechanism of skeletal destruction? Is OAF important (228-230)?

7) How can patients with stable, nonprogressive plasma cell dyscrasias be prospectively distinguished from those with incipient myeloma? How can myeloma be detected at an earlier stage (i.e., lower tumor cell mass)?

8) Which BJP are nephrotoxic? What is the mechanism of renal damage? Which BJP are amyloidogenic? Can in vitro tests for nephrotoxicity and amyloidogenicity be developed? What is the mechanism of tissue deposition as amyloid? Can amyloid fibrils composed of BJP be mobilized from tissues?

9) What is the best therapy for induction? How can remission be made more durable? What are the most effective chemotherapeutic regimens for the "plateau phase"? Will in vitro tests for drug sensitivity become clincally useful (130, 269-279)?

10) What is the mechanism (alkylating agents, extended natural history, etc) for the occasional development of acute leukemia in responding patients? How can the incidence be diminished (170-172,295)?

Elucidation of the answers to these and other questions are critical to increasing our knowledge of this intriguing disorder. In the meantime, it is likely that the study of myeloma will continue to provide important insights to the clinician, the cellular immunologist and the immunochemist.

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a mild normocytic, normochromic anemia (hemoglobin 9.4 hematocrit 30); white cell and platelet counts, as well as calcium, uric acid, BUN and creatinine, were within normal limits. A bone survey demonstrated DJD and diffuse osteoporosis but no lytic lesions. Because of the marked increase in a previously stable spike, a bone marrow was performed in October 1978, which revealed a hypercellular marrow with greater than 50% plasma cells in sheets and clusters. She has been started on chemotherapy with melphalan and prednisone.

Comment: Although most patients with PCDUS do not progress to overt myeloma, a few do. This patient was observed for seven years before myeloma could be diagnosed; periodic re-examination is the only means to identify the change in status.