MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

9/30/71

THE PROTEAN MANIFESTATIONS OF LIGHT CHAIN DISEASE

OUTLINE

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CASE PROTOCOLS

Acute Renal Failure of Unknown Etiology

Case 2. [redacted]

This 59 year-old woman was well until [redacted] 1969 when she developed nausea and vomiting. Her local physician prescribed antibiotics for a urinary tract infection but the nausea persisted. On [redacted]/69 she was admitted to a hospital in [redacted], Texas after having several tarry stools. She was found to be anemic (Hct 25%) and a duodenal ulcer was demonstrated on UGI x-ray. She was given transfusions and also antibiotics for pneumonia. Her BUN on admission had been 48 mg% but repeat on [redacted] was 102 mg%. An IVP performed at that time did not visualize. Retrograde pyelograms on 10/28 were said to be normal. The patient developed recurrent vomiting, back pain and oliguria. On [redacted] she became confused and disoriented and was transferred to [redacted].

On admission here, the pulse was 105/min and respirations 36/min; the temp. and BP were normal. The patient was an obtunded, edematous middle-aged woman in acute respiratory distress. The jugular veins were distended at 45°. Chest examination revealed diffuse rales and rhonchi with dullness at both bases. A crepitant 6 cm mass was noted in the region of the right 9th rib posteriorly. The liver was palpable 5 cm below the RCM (18 cm overall). 2+ presacral and 3+ bilateral pedal edema were noted. Bilateral Babinski signs were present. There were no skin lesions and no significant lymphadenopathy or splenomegaly.

Admission laboratory data included Hgb 10.4, Hct 32, WBC 16.100 with left shift, platelets 260,000, Na 135, K 3.4, CO_2 24, Cl 83, BUN 85, Creat. 13.5, Ca 9.5, P 9.7, uric acid 12.2, pH 7.45, pCO_2 33, pO_2 43 and O_2 sat. 83%. Serum protein electrophoresis showed low albumin (2.5 gm%), increased α_2 globulin and no evidence of a monoclonal spike. Urine showed 3+ protein with negative heat test for Bence Jones protein. The stool guaiac was 3+. Chest film disclosed a bilateral diffuse reticulonodular infiltrate and a questionable lytic lesion of the right posterior 9th rib. Skull films were negative. The urine output decreased from 300 ml/24 hr. to anuria, unresponsive to furosemide. Peritoneal dialysis was begun but the patient continued to have severe respiratory distress with evidence of decreased compliance and persistent abnormalities on chest film. Gastrointestinal bleeding resulted in a fall in Hct from 31% to 25% despite 2 units p.c. On 11/10, peripheral blood smear showed a leukocytosis, 10 nucleated RBC/100 WBC and decreased platelets. The bone marrow was hypercellular and composed of 90% plasma cells in sheets and clusters; many of these cells were plasmablasts. Serum IgG, IgA and IgM levels were markedly decreased; IgD was not detectable. Immunoelectrophoresis demonstrated Bence Jones proteinemia, type kappa. During the ensuing 16 hours, the patient gradually became hypotensive and expired.

Autopsy confirmed the diagnosis of multiple myeloma; the 9th rib lesion was due to a sheet of plasma cells. The patient also had amyloidosis involving the lungs, G-I tract, kidneys, liver and spleen. A recent myocardial infarction and marantic endocarditis were additional findings.

Comment: This patient presented with unexplained renal failure and proteinuria. The latter should have been quantified and defined by means of urine protein electrophoresis and then immunoelectrophoresis. However, an IVP was performed following which the patient developed oliguric renal failure which eventually resulted in her demise. Myeloma was considered in the differential diagnosis of her renal failure but the absence of a monoclonal spike in the serum and the negative Bence Jones test on the urine led her physicians away from that possibility. The diagnosis was finally established 41 days after she entered the hospital in Midland but only 16 hours prior to her death.

Intramedullary Plasmacytoma

Case 3. [redacted]

This 38 year-old woman came to the [redacted] in [redacted] 1970 because of the abrupt onset of left shoulder pain which began after she slipped and bumped the shoulder against a bathroom sink. In retrospect, she admitted having noted a dull aching pain in the shoulder for the previous 5-6 months. Physical exam was negative except for marked local tenderness over the left upper arm without evidence of soft tissue swelling. X-ray revealed a pathologic fracture in the proximal humerus through a lytic defect which was not sharply marginated. Other films, including a bone survey, were negative. The lesion was biopsied and found to be a plasmacytoma. Postoperatively, the patient received Co^{60} therapy. On further evaluation, CBC, ESR, BUN, serum creatinine and calcium were WNL. Serum protein electrophoresis showed decreased albumin (3.0 gm%) and increased α-2 globulin but no suggestion of a monoclonal component. Urine protein was 500 mg/24 hr; the Bence Jones heat test was negative. However, urine protein electrophoresis showed a clear-cut monoclonal component; this was identified as a λ-type Bence Jones protein. The bone marrow contained 25% plasma cells but no sheets of cells were observed.

In [redacted] 1970, the patient underwent a vaginal hysterectomy for carcinoma in situ of the cervix. Her post-op course was uneventful and she was lost to follow-up until [redacted]. 1971 when she came to the clinic because of intermittent low back pain of two months' duration. CBC, ESR, chemistries and bone marrow were unchanged from the previous findings 16 months before. Repeat bone survey was again negative. However, quant. 24 hr. urine protein excretion had increased to 1.2 gm. The serum and urine electrophoretic patterns are shown in Fig. 2. She has recently been started on Alkeran Rx.

Comment: This young woman raises several interesting points about the natural history of plasmacytoma and myeloma. Whether such apparently "solitary" intramedullary plasmacytomas are ever truly isolated tumors is doubtful. The plasmacytosis in her sternal marrow, although not diagnostic, nevertheless suggested a more generalized disease process. Stronger evidence for diffuse disease was generated by the finding of significant Bence Jones proteinuria. The patient remained untreated during the 16 months she was lost to follow-up but even after this interval, her blood and marrow findings had not changed and there was no evidence of additional lytic bone lesions. However, the progressive nature of her plasma cell dyscrasia was supported by the increase in Bence Jones proteinuria. For this reason, chemotherapy with Alkeran was instituted.

Bone Pain Associated with Widespread Osteolytic Lesions

Case 4. [redacted]

This [redacted] 71 year-old woman was in good health until 5 months prior to admission when she abruptly developed pain in the lower left chest. The pain gradually subsided during the next month but then recurred accompanied by severe left arm and hip pain, all of which were markedly worsened by the slightest movement. One month prior to admission she noted a nontender firm lump over the left temporal area which subsequently increased in size. Past history revealed that she had received several X-ray treatments to both breasts in 1948 for "mastitis."

On physical examination, a 2 x 3 cm. firm, fixed nontender mass was present over the left parieto-temporal region. There were small cystic nodules in both breasts but no suggestion of a dominant mass or axillary adenopathy. Marked pain was elicited on even the mildest palpation of the rib cage, left hip or left arm. The neurological exam was unremarkable. Laboratory data included Hgb 11.4, Hct 35, WBC 9.3 with normal differential, platelets 383,000, ESR 89, BUN 21, Creat. 0.9, Ca 12.9, P 4.1 and uric acid 7.1. Serum protein electrophoresis showed low albumin (3.0 gm%), mild increase in α_2-globulin and no evidence of an M-spike. Serum levels of IgG, IgA and IgM were reduced; IgD was not detectable. 1+ protein was reported on urinalysis but the Bence Jones heat test was negative. Urine protein excretion was 600 mg/24 hr. Bone films disclosed widespread lytic defects in skull, ribs and left humerus. A bone marrow aspirate showed sheets and clusters of plasma cells, many of which were primitive and bizarre. Protein electrophoresis of a concentrated urine specimen demonstrated a small amount of albumin and a spike in the fast gamma region; the latter was identified as kappa-type light chains by immunoelectrophoresis. Lambda light chains were not present. The patient was treated with a high fluid intake, analgesics, Alkeran, prednisone and allopurinol. She was discharged with a serum calcium of 11.1 mg% on the 6th hospital day to receive local irradiation for pain relief as an outpatient.

Comment: This patient exemplifies the classical clinical presentation of myeloma. However, because of the absence of a monoclonal spike on serum protein electrophoresis and the negative heat test for Bence Jones protein, the working diagnosis was temporarily shifted to metastatic carcinoma. Since it was necessary to concentrate the urine before performing cellulose acetate electrophoresis and immunoelectrophoresis, the results of these studies were not available for several days. In the meantime, bone marrow aspiration established the diagnosis.

Chronic Renal Failure of Unknown Etiology

Case 7. [redacted]

This 64 year-old woman had been followed at [redacted] for 25 years for luetic heart disease with aortic insufficiency, chronic alcoholism and recurrent pneumonias (1953, 1960 and 1964). In 1964 her BUN was 11 mg%. She came to the [redacted] in [redacted] 1969 because of anorexia, nausea and vomiting and was found to be anemic (Hgb 10.8 gm% Hct 32%) and azotemic (BUN 78 mg%, creatinine 3.2 mg%) with a serum bicarbonate of 16 mEq/L. She was referred to Medicine Clinic where upper G-I and gallbladder films were negative. The patient was not seen again until [redacted] 1970

when she returned with nausea, vomiting and a metabolic acidosis. Physical exam was unremarkable except for the presence of the murmurs of aortic regurgitation and stenosis. There was no bone tenderness and she was not hypertensive. Laboratory data included Hgb 8.1 gm%, Hct 24%, WBC 5500 with normal differential, platelets 144,000/mm^3, BUN 66 mg%, creatinine 5.7 mg%, Na 135 mEq/l., K 5.4 mEq/l, CO_2 10 mEq/l and Cl 116 mEq/l. The serum calcium was 8.6 mg% and the uric acid 9.3 mg%. Urine protein was 2+ by dipstix and 4+ by SSA. Urine for Bence Jones protein was negative by the heat test. The kidneys were only faintly visualized on IVP but appeared to be of normal size. Serum protein electrophoresis demonstrated a ? small abnormal component in the gamma region but no monoclonal spike. The patient was discharged on Shohl's solution on the 7th hospital day with the diagnosis of chronic renal failure of unknown etiology. She was referred to Hematology Clinic where she was seen initially on [redacted]/70. A random urine specimen was positive for Bence Jones protein by the p-toluene sulfonic acid (TSA) test. 24 hr. urinary protein excretion was 4.6 gm. Urine electrophoresis showed a tall symmetrical monoclonal spike in the gamma region (see Fig. 2); immunoelectrophoretic analysis demonstrated marked increase in lambda light chains without evidence of kappa. The patient also was found to have lambda Bence Jones proteinemia. Serum levels of IgG, IgA and IgM were reduced; IgD was undetectable. The ESR was 32 mm/hr and a bone survey was negative but a bone marrow aspirate showed 75% plasma cells in sheets and clusters. Treatment with allopurinol and intermittent Alkeran was instituted in [redacted]. 1970. Despite a CVA in Dec. 1970 and an episode of pneumococcal pneumonia in [redacted]. 1971, the patient has done reasonably well during the past year. When last seen in the clinic on [redacted]/71, the urine protein excretion was 1.4 gm/24 hr., BUN 92 mg%, creatinine 8.6 mg% and uric acid 3.3 mg%. A repeat bone survey was negative for osteolytic lesions.

Comment: The clinical presentation in this patient consisted of gradually increasing renal failure, proteinuria and anemia. The diagnosis became clear when the proteinuria was quantified and defined. The discrepancy between the dipstix and SSA methods is ascribable to the fact that the former does not detect Bence Jones protein while the latter does. Note also the unreliability of the heat test for Bence Jones protein which was negative here as well as in Cases 2-4 above (see also Case 11 below). We have found the TSA method useful as an initial screening test for Bence Jones protein; it is at least as sensitive as the heat test and far easier to perform.

Lanthanic Light Chain Disease in a Patient with SC Hemoglobinopathy

Case 11. [redacted] [redacted]

This 68 year-old [redacted] man came to [redacted] in [redacted]. 1970 complaining of longstanding pain in both hips and intermittent dyspnea which was not associated with cough, sputum, exertion or symptoms of heart failure. Physical examination was negative except for 8 cm splenomegaly. The clinic physician ordered a number of studies including a bone survey and protein electrophoresis of serum and urine. Bone films showed the biconcave contour of the vertebral bodies typical of sickle cell hemoglobinopathy. Multiple areas of increased bone density were noted throughout the skeleton which were felt to be due to healed bone infarcts. Both femoral heads were flattened as a result of ischemic necrosis and there was

secondary degenerative arthritis involving both hips. Because of the splenomegaly, the radiologist interpreted the bone abnormalities as likely resulting from a mixed hemoglobinopathy, possibly S-C. No evidence of lytic bone lesions was seen on the films. The serum protein electrophoresis was unremarkable but electrophoresis of a concentrated urine specimen disclosed a typical M-spike in the beta region.

The patient was hospitalized in [redacted] 1971 for further evaluation. The CBC was normal but a sickle prep was positive and the peripheral smear exhibited the classic changes of S-C hemoglobin. The ESR was 5 mm/hr. The bone marrow showed erythroid hyperplasia with a 2:1 E:G ratio (normal 1:3 to 1:5). Mild plasmacytosis (8%) was present; most of the plasma cells appeared immature. The BUN was 12 mg%, creatinine 1.7 mg%, serum calcium 9.5 mg% and uric acid 7.0 mg%. Serum levels of IgG and IgM were normal; IgA was reduced and IgD was undetectable. Urine protein was reported as Tr by dipstix and the Bence Jones heat test was negative. However, urine protein was 4+ using SSA and the TSA test for Bence Jones protein was positive. Quantitative urine protein excretion was 1.6 gm/24 hr. and repeat urine electrophoresis confirmed the presence of a monoclonal component consisting of type lambda light chains as established by immunoelectrophoretic analysis. A rectal biopsy was negative for amyloid. The patient has been treated with intermittent Alkeran and followed in the Hematology Clinic. His most recent 24 hr. urine protein was 580 mg [redacted]/71).

Comment: The discovery of this patient's asymptomatic plasma cell dyscrasia was fortuitous. Whether a relationship exists between the LCD and his hemoglobinopathy is unknown. This case raises the possibility that occasional instances of LCD may fall into the category of "plasma cell dyscrasias of unknown significance", analogous to the quite common situation encountered with IgG and IgA paraproteins. However, because of the rarity of nonmyelomatous light chain disease and because of this patient's marked Bence Jones proteinuria, it was decided to classify his condition as a malignant plasma cell dyscrasia (i.e., myeloma) although he has neither a diagnostic marrow nor evidence of lytic bone lesions.

Primary Amyloidosis

Case 20. [redacted]

This 59 year-old [redacted] developed a carpal-tunnel syndrome which was surgically relieved in [redacted], Texas in [redacted] 1970. He was then apparently well until [redacted] 1971 when he noted the onset of hoarseness, a thick tongue and bilateral swellings in the submandibular regions. During the next few months, the tongue enlargement gradually progressed to the point where it interfered with swallowing and speech and caused airway difficulties during sleep. In [redacted] 1971, he developed dyspnea on exertion, pedal edema and low back pain which radiated to both thighs. The patient had received a medical discharge from the military in 1942 because of "severe nephritis." Except for a crushed shoulder sustained in a tractor accident in 1966 which required multiple surgical procedures, the past history was otherwise unremarkable.

On physical exam, the vital signs were normal. The patient was a muscular middle-aged white male with slurred speech, obvious macroglossia and edema of the lower extremities. Small purpuric areas were present over the trunk and upper arms but there were no hyperpigmented plaques. The tongue was huge, filling the entire oral cavity and most of the posterior pharynx. The submandibular glands protruded bilaterally but were not increased in size and there was no lacrimal or parotid gland enlargement. The heart was increased in size by percussion and occasional premature contractions were noted. A short grade ii systolic ejection murmur was audible along the left sternal border. There was no lymphadenopathy, ascites or hepatosplenomegaly. Scrotal edema was present as was 2+ bilateral pretibial edema. A bruit was heard over the left iliac and femoral arteries. The neurological exam was negative.

Laboratory data: Hgb 14.2 gm%, Hct 40%, WBC 8200 with normal differential, platelets 265,000/mm^3, ESR 15 mm/hr, BUN 15 mg%, creatinine 0.9 mg%, Ca 9.4 mg%, and uric acid 7.1 mg%. Serum protein electrophoresis showed albumin of 3.7 gm%, slight increase in α-2 globulin and borderline low gamma globulin. Serum levels of IgG, IgA and IgM were reduced; IgD was undetectable. Urine protein was negative by Dipstix but 4+ by SSA and the quantitative urine protein excretion was 4.5 gm/24 hr. Bence Jones protein was present by both the heat and TSA tests. Urine protein electrophoresis demonstrated a typical M-spike in the fast gamma region which accounted for $>$ 90% of the protein present (see Fig. 2). Immunoelectrophoresis of a concentrated urine specimen showed a marked increase in lambda-type light chains, a small amount of albumin and only trace kappa determinants. The patient also was shown to have lambda Bence Jones proteinemia by immunoelectrophoresis. Chest film disclosed cardiomegaly with evidence of early congestive heart failure; upper GI, barium enema, IVP and bone films were negative. The EKG showed nonspecific ST and T wave changes and occasional PVC's; the voltage was normal. A liver scan was negative.

A needle biopsy of the tongue showed marked infiltration with amyloid. Bone marrow aspiration demonstrated 70% plasma cells in sheets and clusters.

The patient was treated with diuretics and has been begun on intermittent Alkeran.

Comment: The picture presented by this man strongly supports the view, advanced by Osserman and others, that primary amyloidosis constitutes one of the malignant plasma cell dyscrasias. Note that the patient did not have anemia, bone lesions or evidence of severe renal functional impairment despite marked infiltration of his marrow by plasma cells and profound Bence Jones proteinuria.

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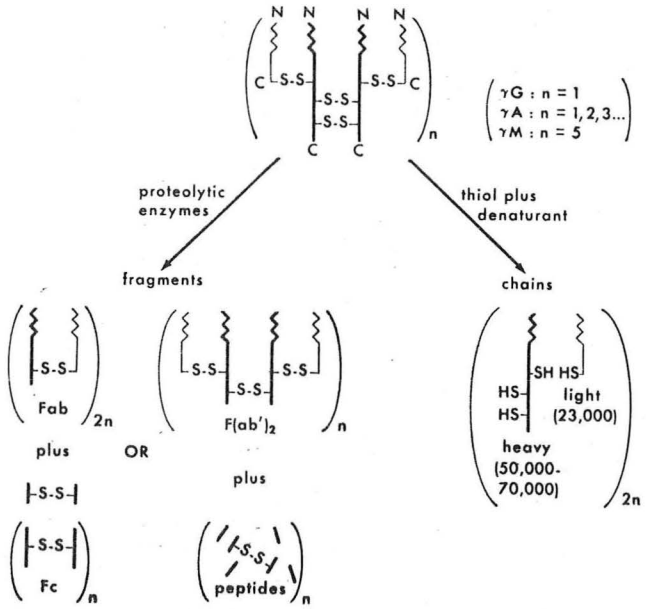
Fig. 1

Basic structure of immunoglobulins. The amino-terminal (N) and carboxy-terminal (C) ends of the polypeptide chains are indicated at the top.



(from Ref. 7)

ELECTROPHORETIC PATTERNS

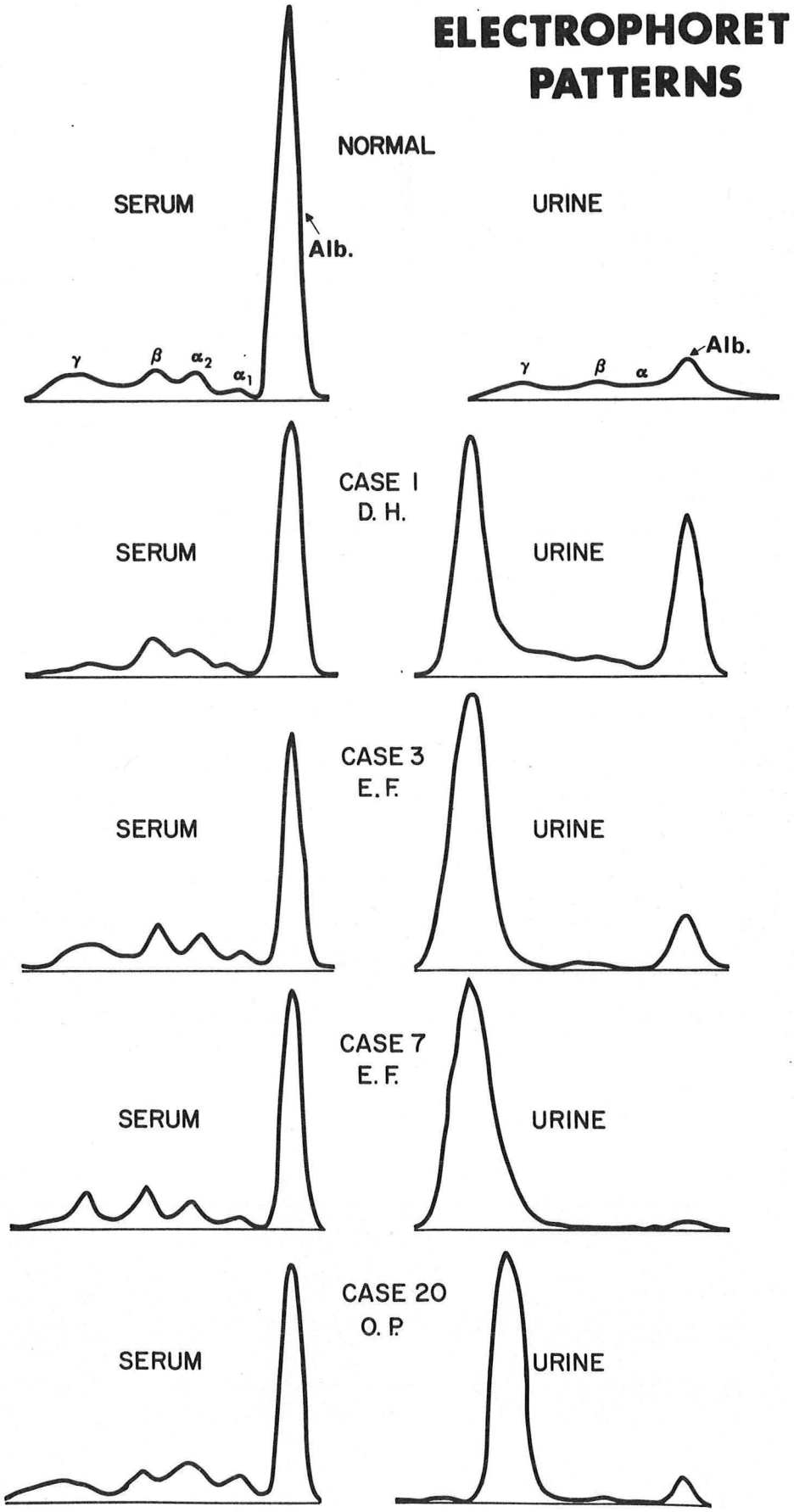


Fig. 2

A. STRUCTURE

As recently as the late-1950's, little was known about the structure of antibody molecules other than they were proteins which migrated in the γ-globulin region on electrophoresis of the serum. However, in 1959, Porter (6) showed that rabbit γ-globulin could be cleaved into 3 different fragments by proteolytic enzymes. Two of these fragments were identical and retained the capacity to combine with antigen (Fab). The third would not combine with antigen but could be readily crystallized (Fc). These observations formed the starting point for a vast number of experimental studies in many laboratories which has led to our present concepts of immunoglobulin structure.

The principal features are shown in Figure 1 and may be summarized as follows:

1) All immunoglobulins have a common fundamental four-chain structure.

2) Two light polypeptide chains of mw $\cong$ 23,000 are linked by single disulfide bonds to two heavy chains of mw 50-70,000.

3) The chains may be separated and characterized by the use of agents which break the interchain disulfides followed by exposure to a denaturant which disrupts the multiple non-covalent interactions between the chains (lower right of Figure 1).

4) All immunoglobulins contain a region in their heavy chains which is highly susceptible to proteolytic enzymes (papain, pepsin, trypsin) such that brief exposure to such enzymes results in cleavage of the molecules into large fragments which are functionally distinct (lower left of Fig. 1). Each Fab fragment contains a single antigen-binding site while the Fc fragments are sometimes crystallizable and contain many of the features common to the individual immunoglobulin classes.

5) Both the heavy and light chains contribute to the Fab fragment and it is likely that portions of both chains form the antibody combining site (8). The amino-terminal 105-110 residues of each light chain vary in primary amino acid sequence while the carboxy-terminal half of the light chain has a constant primary structure within any class (or subclass). Similar variable and constant regions are present in the heavy chains (8,9).

6) The five immunoglobulin classes are defined by structural differences in heavy chains; these may be defined by the use of appropriate antisera specific for each chain.

7) The two light chain types (kappa and lambda) are common to all the heavy chain classes. Normally, the κ:λ ratio is 2:1 (10) but any single Ig molecule is symmetrical, i.e., it bears either 2 κ or 2 λ light chains.

8) Antibody specificity is determined by the primary amino acid sequence (and thus the genetic code) of the variable portions of each chain (8). 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 as yet unclear (9,11).

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B. RELATIONSHIP TO 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, over 125 years ago and thus were among the first proteins described. The paper reporting the initial studies (12) began as follows: "On the 1st of November 1845 I received from Dr. Watson the following note, with a test tube containing a thick, yellow, semi-solid substance:--- 'The tube contains urine of very high specific gravity; when boiled it becomes highly opake; on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but, as it cools, assumes the consistence and appearance which you see: heat reliquifies it. What is it?'" Jones verified the peculiar thermosolubility properties of the protein, subjected it to a careful elementary analysis and concluded that it was the "hydrated deutoxide of albumin."

During the ensuing 115 years numerous attempts were made to define the nature of Bence Jones proteins (over 700 papers appeared on the subject). However, these proteins remained a kind of medical and biochemical curiosity except in the domain of clinical diagnosis: the demonstration of Bence Jones protein in the urine called for the diagnosis of multiple myeloma and such a finding was said to be present in 40-60% of patients with this disorder.

In 1962, the nature of Bence Jones proteins (BJP) was finally clarified by Edelman and Gally (13) who showed that BJ protein shared identical properties (molecular weight, electrophoretic, thermo-solubility and spectrofluorometric) with L chains isolated from that patient's whole myeloma protein and L chains isolated from normal human 7S γ-globulins; H chains shared none of these properties. Gally and Edelman (14,15) later showed that BJP exist as stable dimers in which the two chains are covalently linked by a single disulfied bond, as dissociable dimers, in which the chains are bound by noncovalent bonds, and as monomers. The dimers had a mw of about 45,000 and the monomers of about 23,000. Type kappa BJP exist as both monomers and stable dimers, but type lambda are mainly stable dimers.

Bernier and Putnam (16) confirmed the finding of BJP in urine existing largely as dimers and found that dissolution at high temperature, long considered a specific property of BJP, was shared by many other proteins when the temperature range was extended above 100°C. Transferrin exhibited similar thermolabile characteristics in the usual temperature range for BJP although the temperature of initial precipitation for transferrin was 4-5° higher than for BJP.

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C. SYNTHESIS

Early studies utilizing the incorporation of ^{14}C amino acids supported the conclusion that BJP were synthesized independently rather than being degradation products of the myeloma proteins (17,18). The cellular origin of BJP was later localized to plasma cells in the marrow. In general, one plasma cell at any time in its existence can produce only one class of heavy chain and one class of light chain (19). In the transplantable mouse myeloma system, it was shown that different proteins elaborated by lines originating from the same host contained the same L chain structural variant (20). Such studies have demonstrated that the control of structure of an L chain type is genetic, since the specific protein and none other is isolated from the same tumor during successive transplant generations. The L chain type is, therefore, a heritable genetic marker for the tumor.

There is no evidence to suggest that the homogeneous "paraproteins" produced by individuals with plasma cell dyscrasias are structurally abnormal (8). Moreover, a number of human and murine myeloma immunoglobulins have been shown to possess functional antibody activity (21). Such findings are consistent with the hypothesis that the L chains present in these proteins and the corresponding BJP are representatives of the population of normal L chains present in antibodies. The fact that no two identical proteins have been found in a sample of over 100 human BJP's analyzed has led to the estimate that "at least a few thousand" individual light chain sequences exist in man (22).

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Biosynthetic studies (23,24) have indicated that H and L chains are synthesized independently on ribosomes of different size and that L chains are released from their ribosomes into an intracellular pool. The H and L chains are then assembled into intact 4-chain immunoglobulin molecules. The carbohydrate moiety is attached during the 20-30 min lag period which occurs prior to secretion from the cell.

Multiple variables influence our ability to identify the presence of a paraprotein in serum or urine, particularly the metabolic properties of the protein (see section I-D below) and the methods employed for its detection (see section I-E). The failure to identify a component in serum or urine does not necessarily signify the absence of synthesis and secretion of that component at the cellular level. Three basic patterns of chain synthesis were observed in a recent study of immunoglobulin production by malignant human plasma cells from 18 myeloma patients in short-term tissue culture (25):

1. extreme unbalanced synthesis with production of L chains only (2 patients)

2. unbalanced synthesis with excessive production of free L chains (12 patients)

3. balanced synthesis with production of equal amounts of H and L chains (4 patients).

Of interest was the finding that Bence Jones proteinuria was not detected (by immunologic methods) in four of the twelve patients in Group 2 although excess free L chains were synthesized and secreted at the cellular level. Moreover, one of the patients in this group was classified as having lambda light chain disease on the basis of serum and urine studies although his plasma cells produced IgG,λ (plus excess free λ chains) in culture.

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D. METABOLISM

The metabolic fate of Bence Jones protein as well as isolated normal L chains differs strikingly from that of intact immunoglobulin molecules. Substantial evidence is available which indicates that a significant proportion of Bence Jones protein is catabolized, the remainder being excreted in the urine. The kidney appears to be the principal catabolic site.

Meyer and Putnam (26) injected labeled human BJP into rabbits and found that only about 50% of the injected dose was excreted intact in the urine. Radioactivity measurements of various organs demonstrated highest specific activity in the kidneys. Similar findings were reported in a study of the metabolism of BJP in humans (27). The survival of labeled BJP was exceedingly short and from 50-90% of the overall metabolism was accounted for by endogenous catabolism, the remainder being excreted as proteinuria. Subjects with normal renal function catabolized 10-40% of the intravascular pool of BJP per hour. Lower catabolic rates were observed in patients with renal functional impairment. In myeloma patients with BJ proteinuria, the relative contributions of catabolism and of urinary loss to the removal of injected labeled BJP from the blood depended on the quantity of their own BJP synthesized and on the renal status of the patient.

Active endogenous catabolism also was shown to be the major factor in the metabolism of injected kappa and lambda human BJP's in mice since excretion as proteinuria accounted for $< 25\%$ of the overall metabolism (28). The catabolic rate was reduced tenfold in nephrectomized mice as compared with unoperated and ureter-severed controls indicating that the kidney was the major site of breakdown of BJP. In both humans and mice the fractional catabolic rate of BJP and of isolated L chains was 100 times that of intact IgG molecules. IgG survival was normal in nephrectomized mice and humans with renal disease indicating that the kidney does not play a significant role in the catabolism of this protein. Essentially normal survival of albumin, IgA, IgM and Fc_γ has also been demonstrated in nephrectomized mice (29).

Waldmann and co-workers have studied L chain metabolism in mice with experimentally-induced (by maleic acid) Fanconi syndrome (29,30). Maleic acid treatment retarded L chain catabolism to about the same extent as did complete nephrectomy suggesting that the renal catabolic site was located in the proximal tubules. Overall metabolism was unchanged, however, since the reduction in endogenous catabolism was balanced by increase in proteinuria.

Immunoglobulin light chains are not the only molecules catabolized by the kidney; similar nephrectomy experiments have demonstrated that the catabolic rate of other small proteins (lysozyme, ribonuclease) is markedly reduced. It is possible,

therefore, that many proteins small enough to pass through the normal glomerular basement membrane are catabolized by the renal tubules. These studies have prompted the formulation of a physiologic model for the manner in which L chains and presumably other low molecular weight proteins are handled by the kidney in various kinds of renal disease (Table I).

TABLE I. Renal Handling of Low Molecular Weight (< 50,000) Proteins in Renal Disease (29,30).

Type of Renal Functional Impairment	Serum Level	Endogenous Catabolism	Fractional Proteinuric Rate*
Pure glomerular	N	N (?)	N
Pure tubular (normal GFR)	N	↓	↑
Chronic renal failure (nephron loss; GFR)	↑	↓	↓

* % i.v. pool/hr (=fractional metabolic rate x % of overall metabolism resulting from proteinuria)

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E. EXCRETION

1. Methods of detection

a) Dipstix do NOT react with BJP and are, therefore, USELESS for its detection. Sulfosalicylic acid (SSA) does precipitate BJP as well as other urine proteins and is a valuable screening test. However, false

positive results may occur in the presence of X-ray contrast media, tolbutamide, penicillin and sulfonamides (31). Quantitative determination of the 24 hr urine protein excretion remains the most valuable test for the detection of significant (> 200 mg/24 hr) proteinuria.

b) BJP's were originally discovered because of their unusual solubility characteristics at relatively low temperature (12). On heating, they precipitate from solution between 50 and 60°C. and redissolve between 90 and 100°C. While many other proteins exhibit similar thermal properties at higher temperatures (16), the range noted above is characteristic for BJP. The precise conditions for demonstration of thermosolubility vary from one BJP to another. Thus some BJP's which precipitate between 50 and 60°C. do not redissolve completely on boiling.

In order to obtain optimal results with the heat precipitation test, strict control of pH and ionic strength is essential (32). Although Snapper has long advocated a modified heat test (33), even he admits that "most laboratory reports about the presence of Bence Jones proteins are misleading" (4). We certainly agree and have found the p-toluene sulfonic acid (TSA) test (34) of much greater value as a screening procedure for BJP. The test is performed by adding 1 ml TSA reagent slowly (over 15-30 seconds) to 2 ml of urine; any precipitate visible within five minutes is a positive result. This method can detect as little as 30 mg% BJP and albumin does not precipitate in concentrations as high as 25 gm% (35). It should be emphasized that a positive test does not make the diagnosis of myeloma or any other plasma cell dyscrasia but only indicates the presence of increased amounts of free L chains in the urine.

c) Electrophoretic and immunologic analyses are the most sensitive and specific methods available for the identification of BJP (36-39). Assessment of heterogeneity is most readily accomplished by means of zone electrophoresis on various supporting media, cellulose acetate being the most widely used. Specific identification of immunologic class (kappa or lambda) is made by using appropriate antisera in immunoelectrophoretic or double diffusion-in-agar (Ouchterlony) assays.

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38. Zelkowitz, L. and Yakulis, V. Immunologic methods for detection and quantification of Bence Jones Proteins, J. Lab. Clin. Med. 76:973, 1970.

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2. Light chain excretion in normals and patients with conditions other than plasma cell dyscrasias.

Shortly after the recognition that Bence Jones proteins were immunoglobulin L chains, the finding of small but significant amounts of free L chains in the urine of normal subjects was reported (40). The normal excretion of urinary L chains may be as high as 50 mg/24 hr. (41). In contrast to the situation in the plasma cell dyscrasias, both types (kappa and lambda) of L chains are present and the usual ratio (κ:λ =2:1) is maintained. Increased levels of urinary L chains have been observed in patients with various immune-related disorders including rheumatoid arthritis (42), homograft rejection (43) and leukemia-lymphoma (41). Free urine L chains have also been found in patients with acquired hypogammaglobulinemia although present in only about one tenth the average normal amount (44). Urinary L chain paraproteins have been described very rarely in patients with lymphoma (4,45).

Although free L chains and albumin account for a large proportion of the total urinary protein, it is now clear that trace amounts of nearly every plasma protein are present in normal human urine (46).

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3. Light chain excretion in plasma cell dyscrasias.

In these monoclonal disorders, the urinary L chain excretion is due to a single light chain class, either kappa OR lambda but not both. The incidence of Bence Jones proteinuria in patients with IgG or IgA myeloma is usually stated to be 20-40% (4,5). However, using sensitive immunochemical techniques, Dammacco and Waldenstrom (47) found that two-thirds of 46 patients with IgG or IgA myeloma had demonstrable Bence Jones proteinuria; only half of these had positive heat tests (see Table II).

TABLE II. Incidence and Amount of Bence Jones Proteinuria (from Ref. 47)

Heat test		Combined electrophoretic and immunoelectrophoretic analysis of concentrated urines		Amount of Bence Jones proteinuria (mg/100 ml)	
Positives	%	Positives	%	Mean	Range
Benign monoclonal gammapathies (42 patients)					
1	2.3	10	23.8	2.3	1.4-5.8
Myelomatosis (46 patients)					
15	32.6	31	67.3	180	20-1000
Macroglobulinemia (10 patients)					
2	20.0	6	60.0	110	42-440

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II. LIGHT CHAIN DISEASE

A. DEFINITION

Light chain disease (LCD) constitutes that subset of multiple myeloma in which the only detectable monoclonal protein abnormality consists of the presence of a single L chain class of restricted electrophoretic mobility in urine and, less commonly, in serum. For this reason, it is frequently difficult to diagnose. LCD accounts for 20-25% of cases of myeloma and, by a variety of criteria, represents the most malignant form of this disorder. Whether LCD ever exists as a stable, nonprogressive plasma cell dyscrasia is unclear. If such a variant does occur, it is very rare.

B. CLASSIFICATION OF PLASMA CELL DYSCRASIAS

Plasma cell dyscrasia is the term generally employed to signify a broad range of pathologic conditions and biochemical abnormalities which result from an unbalanced or disproportionate proliferation of one or a limited number of clones of cells which ordinarily synthesize immunoglobulins (1,5).

Although these disorders are associated with diverse clinical manifestations, they typically exhibit the common features of

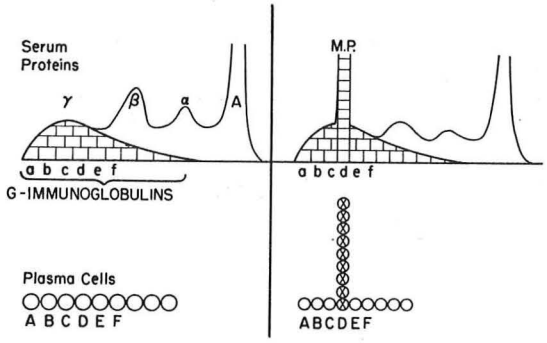
1) proliferation of plasma cells, either local or diffuse

2) elaboration of a homogeneous M-type (monoclonal) protein

3) decreased production of normal immunoglobulins (frequent but not invariable).

The normal plasma cell population may be regarded as heterogeneous with individual clones of plasma cells producing different immunoglobulins. The usual heterogeneous (as defined by electrophoretic mobility as well as by many other chemical parameters) immunoglobulin population thus represents a family of somewhat different molecules produced by a normal plasma cell pool. A disproportionate proliferation of one clone of plasma cells from this population results in a corresponding increase in its secreted molecular product in the serum. This is ordinarily observed as a homogeneous M-spike on the electrophoretic pattern (see Fig. 3).

Fig. 3 (from Ref. 1)



In actuality, the extent of the proliferative abnormality in the various plasma cell dyscrasias ranges from autonomous neoplastic proliferation in typical multiple myeloma to apparently benign and stable dyscrasias manifested principally by their associated immunoglobulin abnormalities. Although some of the latter group may be nonprogressive (and ? protective), others undoubtedly represent instances of incipient or premyeloma that happened to be discovered prior to becoming symptomatic. At present, it is impossible to predict which course will be taken by any individual patient and thus the term "plasma cell dyscrasia of unknown significance" (PCDUS) is preferred to the possibly misleading "benign" or "essential" labels which others have used in the past.

TABLE III. PLASMA CELL DYSCRASIAS

Modified from Osserman, refs. 1,5.

Multiple myeloma
IgG, IgA, IgD, IgE
LIGHT CHAIN DISEASE

Waldenstrom's macroglobulinemia (IgM)

Heavy chain diseases
Gamma-chain disease (Fc_γ)
Alpha-chain disease (Fc_α)
Mu-chain disease

"Primary" amyloidosis

Lichen myxedematosus (papular mucinosis)

Plasma cell dyscrasias of unknown significance (PCDUS)
-associated with lymphoreticular neoplasms
-associated with non-lymphoreticular neoplasms
-associated with chronic R-E stimulation
-associated with various other disorders
-in apparently healthy individuals (age-related incidence)

C. INCIDENCE

The frequency of patients with LCD has been reported to vary between 8% and 30% of patients with serum and urine paraproteins in various series (3-5, 48-51). The lower incidence (8-15%) is restricted to those reports which include all plasma cell dyscrasias. When only proven cases of myeloma are analyzed, the incidence of LCD rises to 20-25%. Thus 19% of 212 cases of myeloma in the British series were due to LCD (50) and 25.1% of 351 myeloma patients in Osserman's series had LCD (5). Our own experience during the past two years is quite similar (Table IV).

TABLE IV

DALLAS PATIENTS WITH

PARAPROTEIN ABNORMALITIES

7/1/69-9/15/71

	No.	MM	PCDUS
IgG	80	49	31
IgA	19	15	4
IgD	2	2	0
LCD	22	22	0
	123	88	35

LCD/MM = 22/88 = 25.0%

LCD/PCD = 22/132* = 16.4%

* Includes 9 patients with macroglobulinemia

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It has been known for over 25 years that Bence Jones proteinuria was present without hypergammaglobulinemia in some myeloma patients. Excessive L chain production was the only demonstrable paraprotein abnormality in 9 of 10 patients with Bence Jones proteinemia reported by Solomon and Fahey (52). The name "light chain disease" was applied to this form of myeloma by Williams et al. (53) following the description of the first cases of heavy chain disease.

At least some cases of "myeloma without a paraprotein" reported in the older literature likely represented cases of LCD in which the Bence Jones protein was missed. Such reports are now quite uncommon (54,55) and not a single case of this kind was found in 563 myeloma patients from two of the best recent series (5,50).

Whether or not LCD ever occurs as a nonprogressive (nonmyelomatous) plasma cell dyscrasia is an unresolved question. Only a very few such cases have been reported (5,56,57) and they must be extraordinarily rare.

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D. DALLAS SERIES

Since July 1969 we have seen 22 patients with light chain disease. As illustrated by the case protocols and Table V, the initial clinical presentation and laboratory findings in these patients constituted a vast array of abnormalities, many of which did not immediately suggest the diagnosis of myeloma. The extent to which the disease was unsuspected may be roughly gauged by the fact that ten of the patients underwent IVP's during or just preceding the admission in which the diagnosis was eventually established. Although the serum electrophoretic patterns were not usually normal, in no case was an M-spike present. Moreover, the Bence Jones heat test was reported as positive in only six instances.

In general the physical exam was not helpful unless bone pain was present. As in other myeloma patients, lymphadenopathy and splenomegaly were usually absent. Rouleaux was not a feature of the peripheral smear in most patients; the ESR (Westergren) was > 50 mm/hr in only 4 of 12 patients.

Serum and urine samples on each patient were examined in the Hematology Research Laboratory except in the case of Patient #2 (L.B.) where no urine was available. Serial specimens have been provided on 14 patients. Cellulose acetate electrophoresis of serum and concentrated urine, immunoelectrophoresis and quantitative determination of serum immunoglobulins were performed.

The data on the entire group are summarized below according to incidence among the two L chain classes.

	Total	Type Kappa	Type Lambda
	22	11	11
Sex ratio M:F	13:9	6:5	7:4
Ave. age	57	54	61
Initial clinical presentation			
Bone pain	10	6	4
Renal failure	4	1	3
Bone pain + renal failure	2	2	0
Misc.	6	2	4
Anemia	12	5	7
↑ BUN	9	5	4
↑ Creatinine	13	5	8
↑ Calcium	6	4	2
↑ Uric acid	13	7	6
> 50% plasma cells	12	4	8
< 5% plasma cells	4	4	0
Lytic bone lesions	15	9	6
↓ Serum IgG, IgA, IgM			
3/3 ↓	14	7	7
2/3 ↓	3	1	2
1/3 ↓	3	2	1
0/3 ↓	2	2	0
$\bar{m}$ 24 hr protein excretion	3.1 gm	1.5 gm	4.5 gm
Bence Jones proteinemia	16	6	10
Amyloid	3	1	2
Plasmacytoma	5	3	2

The principal differential diagnostic consideration of LCD is IgD myeloma. Although this type constitutes only about 1-2% of cases of myeloma, it is necessary to rule out the presence of an IgD paraprotein since the serum levels are often relatively low and marked Bence Jones proteinuria (80-90% λ) is characteristic (58). IgD was detectable in the serum of only three of our patients; in each case the quantitative level was within normal limits and immunoelectrophoresis revealed no evidence of an IgD paraprotein.

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E. NEPHROTOXICITY OF BENCE JONES PROTEINS

Renal functional impairment occurs in the majority of myeloma patients and an association with Bence Jones proteinuria has long been implied. The typical histologic finding in "myeloma kidney" is extraordinary cast formation. These casts spread up into the proximal tubules thus apparently obstructing the nephron and resulting in atrophy of the tubular epithelium. The casts characteristically appear eosinophilic and laminated; frequently giant cells are seen within the tubular lumen surrounding a cast. Such plugging of the tubules is thought by some to be the principal cause of renal failure in myeloma (59).

Evidence for the direct nephrotoxicity of Bence Jones protein is sparse (4,5,59-61). In an immunofluorescent study of myeloma kidney in nine patients (three of whom had LCD), positive staining for many plasma proteins including albumin, fibrinogen, IgG and both types of L chains was observed in tubular casts (61). Similar diverse staining characteristics were seen in casts examined from five patients with other kinds of renal disease. Tubular epithelial cell atrophy, rather than tubular casts, directly correlated with clinical evidence of renal insufficiency in the myeloma patients.

On the other hand, Bence Jones proteinuria has occasionally been associated with specific defects in proximal tubular reabsorptive mechanisms. Ten cases of myeloma with co-existent acquired Fanconi syndrome have been reported (4). In several instances, cytoplasmic needle-like inclusion bodies were present in the proximal tubular cells. Similar cytoplasmic inclusions were noted in the plasma cells from one such patient (62). Recent experimental evidence also suggests that BJP's may produce direct functional impairment in renal cortical slices in vitro (63).

Dehydration appears to play a major role in the development of acute renal failure following intravenous pyelography in occasional myeloma patients. Although certain older X-ray contrast media have been demonstrated to cause in vitro precipitation of Bence Jones protein from acidified urine, those contrast agents in current use evidently do not (64). Intravenous pyelography has been performed on over 150 myeloma patients without adverse effects (65,66). It would appear that if an IVP is indicated in a myeloma patient or suspect, the likelihood that renal failure will ensue is small provided adequate hydration is maintained.

In summary it is difficult to come to any firm conclusions about the nephrotoxic properties of BJP's. Certain BJP's may directly contribute to renal functional impairment. However, the fact that apparently normal renal function persists in many cases of prolonged and profound Bence Jones proteinuria indicates that not all BJP's are nephrotoxic (5). Most cases of renal failure in myeloma are probably due to multiple factors, particularly hypercalciuria and dehydration. Hyperuricemia, amyloid and pyelonephritis are also potential contributory factors in myeloma patients.

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F. AMYLOID

A substantial amount of evidence is available which links some forms of amyloidosis to plasma cell dyscrasias (1-5). Amyloid occurs in 10% of patients with overt myeloma and in a somewhat smaller percentage of cases of Waldenstrom's macroglobulinemia. In these circumstances, the amyloid is deposited in the so-called "primary" distribution, i.e., in tongue, heart, G-I tract, connective tissue, skin and peripheral nerves. The liver, spleen, kidneys and adrenals tend to be involved to a lesser extent than in "secondary" amyloidosis but there is considerable overlap (67). It is also clear that a sizable proportion of cases of idiopathic primary amyloidosis have an associated plasma cell dyscrasia (68-70). For several years Osserman has implicated gamma globulin components, particularly L chains, in the pathogenesis of amyloidosis because of their presence in amyloid infiltrates as demonstrated by immunochemical techniques. Although some investigators (71) have firmly opposed such a hypothesis, recent experimental data strongly support it. Glenner and co-workers have performed amino acid sequence studies on two amyloid fibril proteins and shown that the amino-terminal 30 residues of both proteins are essentially identical to the comparable region of a kappa Bence Jones protein (72).

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G. THERAPY AND PROGNOSIS

1. General measures

Proper management unquestionably improves the quality of life in patients afflicted with myeloma. The importance of adequate hydration and ambulation cannot be overemphasized! Optimal use of effective analgesics, orthopedic supports and radiotherapy to localized areas of involvement provide significant relief of pain in the majority of patients. Corticosteroids are valuable adjuncts if hypercalcemia is present. All of these measures are critical in many patients if they are to survive long enough to achieve a remission with chemotherapy. Peritoneal or hemodialysis should be considered in those patients presenting with acute renal failure as it may be reversible (73).

2. Chemotherapy

Many studies have demonstrated the efficacy of melphalan (l-phenylalanine mustard, Alkeran) given either by continuous or intermittent dosage regimens (74-77). Cyclophosphamide (Cytoxan) is an apparently comparable agent (77).

The prognosis of patients with LCD is worse than in patients with either IgG or IgA myeloma (50). Thus light chain myelomas grow fastest and are associated with a higher frequency of osteolytic lesions, hypercalcemia, renal failure and amyloidosis. The most important factors affecting the prognosis of myeloma patients are the initial levels of the BUN and serum albumin (77,78). Although some workers (79) have maintained that patients with lambda Bence Jones proteins respond to therapy less well than those with type kappa, this point remains controversial (78).

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