Structural Identity of Bence Jones and Amyloid

Fibril Proteins in a Patient

with Plasma Cell Dyscrasia and Amyloidosis

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A B S T R A C T The partial amino acid sequence of the amyloid fibril protein isolated from the small intestine of a patient with plasma cell dyscrasia and associated amyloidosis has been determined and compared with the sequence of the κ-type Bence Jones protein isolated from the urine of the same patient. Identical sequences were observed for the 27 amino-terminal residues that could be compared. The C-terminal tryptic peptide of the amyloid protein was identical with that of the Bence Jones protein. Apparent molecular weights and amino acid compositions of the Bence Jones and amyloid proteins were similar. It appears, therefore, that the predominant protein present in the amyloid deposits in this patient was an intact κ-type light polypeptide chain that was identical with the urinary Bence Jones protein.

INTRODUCTION

Considerable information concerning the nature and structure of amyloid protein has been acquired in the past few years. Available evidence indicates that in many instances, the major protein in amyloid fibrils is some portion of an immunoglobulin polypeptide chain. Amino acid sequence studies have shown that the amino-terminal sequence of some amyloid fibril proteins is homologous with that of light polypeptide chains (1, 2). Moreover, it

is possible to create fibrils having the tinctorial, ultrastructural, and crystallographic properties of amyloid fibrils by proteolytic digestion of certain Bence Jones proteins (3).

Immunoglobulin-related amyloid fibril proteins have been found in a number of clinical settings, including so-called "primary" amyloidosis (2, 4, 5), amyloidosis secondary to epidermolysis bullosa and tuberculosis (2, 4) and isolated nodular pulmonary amyloidosis (6, 18). Information concerning the sequence of amyloid fibril protein from patients with plasma cell dyscrasia and amyloidosis has, however, not been available. It is of some importance to establish that, in a patient with plasma cell dyscrasia, circulating homogeneous immunoglobulin, and amyloidosis, the immunoglobulin of the amyloid fibril is identical with the circulating homogeneous immunoglobulin or at least a portion of it. Failure to demonstrate such a relationship would have important implications for the pathogenesis of amyloid deposits (7).

It was possible to obtain sequence information for the Bence Jones protein and the amyloid protein of the same patient since one of us (Dr. Osserman) had studied a patient who died in 1958 with plasma cell dyscrasia, κ-type Bence Jones proteinuria, and amyloidosis (case 14 in reference 8). The sequence of the Bence Jones protein from this patient has been determined in another laboratory (9).[1] When the patient died, organs containing amyloid deposits were removed at autopsy and stored in the frozen state. This paper will present evi-

[1] Whitley, E. J., and F. W. Putnam. Personal communication.

dence indicating the identity of the urinary Bence Jones protein with the major protein isolated from a concentrate of the patients' amyloid fibrils.

METHODS

Isolation of Bence Jones protein. The Bence Jones protein was precipitated from whole urine by 2.8 M ammonium sulfate and stored as a paste at $-20°C$. At the time of these experiments, the precipitate was dialyzed against water and lyophilized. Lyophilized material was dissolved in 0.2 M Tris-HCl pH 8.0 buffer and subjected to gel filtration on Sephadex G-200. Eluted material was tested by double diffusion in agar with specific antisera, and the fractions containing κ-type light chains were pooled, dialyzed against water, and lyophilized.

Isolation of amyloid fibril protein. A segment of small intestine measuring 20 cm in length was the source of the amyloid fibril concentrate. Previous microscopic examination revealed extensive replacement of the subserosa by amyloid deposits as defined by green polarization birefringence after Congo red staining (10). The frozen small intestine was hydrated in saline buffered to pH 7.1 with 0.1 M sodium phosphate (phosphate-buffered saline, PBS).[2] The amyloid-laden subserosal tissue was dissected from the muscularis, homogenized in PBS, and a preparation having the typical tinctorial (10), crystallographic, and electron microscopic (3) characteristics of an amyloid fibril-rich concentrate was obtained as previously described (4). The amyloid fibril concentrate was lyophilized and completely dissolved in 6 M guanidine-HCl containing 0.1 N Tris-HCl, pH 8.0 and made 0.01 M in dithiothreitol with agitation under nitrogen at 25°C for 3 h (11). The solution was diluted to 5 M guanidine-HCl in 1 N acetic acid, and gel filtration chromatography was performed sequentially using Sepharose 4B and Sephadex G-100 columns equilibrated with 5 M guanidine-HCl in 1 N acetic acid (4). The major protein fractions obtained were dialyzed exhaustively with distilled water and lyophilized. The yield of purified amyloid fibril protein was calculated on the basis of dry weight and Lowry protein determinations of the lyophilized crude amyloid fibril concentrates, and of the lyophilized purified amyloid fibril protein.

Peptide maps. The purified amyloid and Bence Jones proteins were reduced with 0.001 M dithiothreitol and alkylated with 0.01 M iodoacetamide. Reduced, alkylated proteins were digested with trypsin (Worthington Biochemical Corp., Freehold, N. J., TPCK trypsin) at a protein to enzyme ratio of 100:1 at pH 8.7 in 0.1 N ammonium bicarbonate buffer. Analytic maps were prepared by spotting 2 mg of the digest on Whatman 3 M paper. Descending chromatography was in water, butanol, and acetic acid (40:27:8) for 20 h, and was followed by electrophoresis in pH 3.5 buffer at 3000 V for 50 min. Papers were stained with collidin-ninhydrin. Preparative peptide maps were prepared by spotting 5 mg of digest on Whatman 3 M paper. Chromatography and electrophoresis were as above. Peptides were located by lightly spraying the paper with a mixture of 75 cm³ of 99% ethanol and 25 cm³ of 2 M acetic acid, to which was added 50 mg of ninhydrin. Peptides were cut out and eluted with water in a moist chamber.

Polyacrylamide disc gel electrophoresis. Studies were performed with proteins reduced and alkylated by the proce-

[2] *Abbreviations used in this paper:* PBS, phosphate-buffered saline; PTH, phenylthiohydantoin; SDS, sodium dodecyl sulfate.
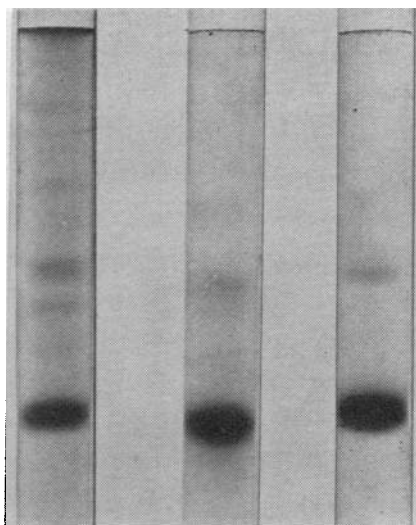

FIGURE 1 Acrylamide gel electrophoresis on 12% gels, in 0.1% SDS, 4 M urea buffered at pH 7.1. Left, Tew amyloid fibril concentrate before gel filtration; middle, purified Tew amyloid; right, purified Tew Bence Jones protein. Anode is to the bottom.

dure described above (peptide maps), as well as with non-reduced and alkylated preparations. Samples of the amyloid fibril concentrate, major amyloid fibril protein, and Bence Jones protein were dissolved at a concentration of 2–8 mg/ml of 8 M urea buffered to pH 8.8 with 0.1 N Tris-HCl containing 50 mM dithiothreitol and incubated at 37°C for 30 min. An equal volume of 8 M urea buffered to pH 7.1 with 0.1 N sodium phosphate containing 50 mM dithiothreitol and 2% sodium dodecyl sulfate (SDS) was added. Gels were prepared with 12% polyacrylamide with a 37:1 monomer to bis ratio, 0.1% N, N, N', N'-tetramethylenediamine in a buffer containing 0.1% SDS in 4 M urea adjusted to pH 7.1 with 0.1 M sodium phosphate, and polymerization was performed using 0.05 vol of a 1% ammonium persulfate solution. Upper and lower electrode compartments contained the gel buffer made 1% in β-mercaptoethanol. Bromphenol blue was used as a tracking dye. A 30–40 μl sample was applied and electrophoresis performed at 3 mA per tube for 16 h. The gels were washed with 50% methanol in 10% acetic acid for 3 h and stained with Coomassie blue.

Amino acid composition. Samples of the purified amyloid fibril and Bence Jones proteins were hydrolyzed in 6 N HCl under vacuum at 110°C for 24 h. Hydrolyzed samples were flash evaporated and analyzed on an amino acid analyzer (Beckman model 120C, Beckman Instruments, Inc., Fullerton, Calif.).

Amino acid sequence analysis. The amino-terminal sequence of the purified amyloid fibril protein was obtained with a protein sequencer (Beckman model 890). Reagents were sequencer-grade chemicals used as obtained from Beckman Instruments, Inc., except that ethyl acetate solvent was made 0.1% with aldehyde-free acetic acid, and 10 mg of dithioerythritol was added to each 950 ml of butyl chloride solvent. The thiazolinone derivatives obtained from the sequencer were converted to phenylthiohydantoin (PTH) amino acids with 1 N HCl at 80°C for 10 min. PTH amino acids were identified on a gas chromatograph (Varian model 1840, Varian Associates, Walnut Creek, Calif.) (12).
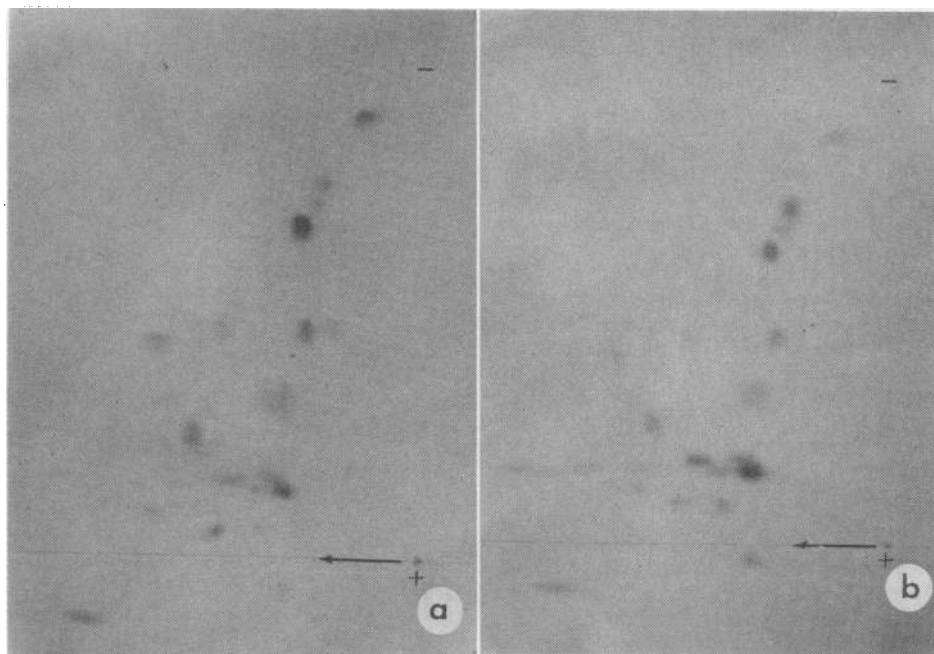
FIGURE 2 Peptide maps of Tew amyloid and Bence Jones proteins. Reduced and alkylated proteins were digested with trypsin, and subjected to descending paper chromatography followed by electrophoresis at pH 3.5. *a*, amyloid; *b*, Bence Jones. Streak in lower left is chromatography marker. Arrow shows direction of chromatography.

A portion of each PTH amino acid sample was converted to the free amino acid by hydrolysis with 6 N HCl at 150°C for 20 h. Free amino acids were identified by analysis on the amino acid analyzer.

RESULTS

The amyloid fibril concentrate consisted of a number of proteins before gel filtration, as evidenced by the eight or more protein-staining bands seen on SDS acrylamide gel electrophoresis (Fig. 1, left). The most heavily staining of these bands, as well as two lighter staining bands of higher molecular weight, were also detected in the purified amyloid preparation (Fig. 1, middle). These results are consistent with the conclusion that the major protein component of the amyloid fibril concentrate is present in the purified amyloid preparation.

Yields were calculated, both on the basis of dry weight and as protein assayed by the Lowry method. The purified major protein fraction represented 42.5% by dry weight and 49.2% by protein determination of the crude amyloid fibril concentrate. Allowing for losses in dialysis and handling, it is therefore estimated that the final product represents at least 60% of the protein present in the amyloid fibril concentrate. These data are also consistent with the conclusion that the purified preparation represents the major protein component of the amyloid fibril concentrate.

The isolated, native Bence Jones protein gave three bands on SDS acrylamide gel electrophoresis. These bands had mobilities identical with those of the purified amyloid protein (Fig. 1, middle and right), indicating that proteins of similar molecular weights were present in these two preparations. It should be noted that during the isolation procedure, amyloid fibril protein was not alkylated after reduction by dithiothreitol. Alkylation was avoided in order that performic acid oxidations and identification of the C-terminal tryptic peptide could be carried out. However, after reduction and alkylation of the amyloid and Bence Jones proteins, SDS acrylamide gel electrophoresis showed only a single band corresponding in mobility to that of the lowest molecular weight protein, and electrophoresis of a mixture of the amyloid fibril and Bence Jones proteins also showed only a single band. This indicates that the higher molecular weight constituents in the nonreduced and alkylated preparations were disulfide-linked polymers of approximately the same size in both the amyloid and Bence Jones preparations.

Additional studies were performed to compare the structural characteristics of the purified amyloid fibril and Bence Jones proteins. Both preparations were reduced and alkylated, digested with trypsin, and studied by peptide mapping at pH 3.5. The maps show minor variation in the intensity of the spots, but within the lim-

its of the technique, the two maps appear to be identical (Fig. 2).

The purified amyloid fibril and Bence Jones proteins were hydrolyzed in 6 N HCl and amino acid compositions determined. The compositions are quite similar (Table I), again indicating the close structural relationship between the amyloid fibril and Bence Jones proteins.

The amino acid sequence of the purified amyloid protein was determined for the amino-terminal 27 residues and is compared with the sequence of the Bence Jones protein (Fig. 3), which was determined by Doctors Whitley and Putnam (9).[3] As can be seen, the amyloid fibril protein is homogeneous, and the sequence of the amyloid and Bence Jones proteins are identical. The yield of the first amino acid was 40% of theoretical, a yield similar to that obtained wtih known purified proteins treated in the same manner, indicating that the protein being sequenced was the major protein present in the purified amyloid fibril preparation. Repeated attempts to extend the sequence past position 27 were unsuccessful, suggesting that the amino group of the glutamine at position 27 probably becomes blocked during the chemical reactions, resulting in a blocked N-terminus which is unreactive with phenylisothiocyanate. Similar problems were encountered in sequencing the Bence Jones protein.[3] These results indicate that the amyloid

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[3] Whitley, E. J., and F. W. Putnam. Personal communication.

TABLE I

Amino Acid Composition of Tew Amyloid and Bence Jones Proteins

	Bence Jones	Amyloid
	mol/100 mol	
Lys	5.2	5.0
His	1.4	1.4
Arg	3.9	3.8
Asp	9.0	9.0
Thr	6.7	6.7
Ser	12.3	11.5
Glu	12.7	13.0
Pro	6.2	6.1
Gly	6.7	7.1
Ala	6.4	6.6
Val	7.5	7.5
Met	0.97	0.99
Ile	3.2	3.3
Leu	10.0	9.9
Tyr	3.4	3.6
Phe	4.4	4.5

Proteins hydrolyzed in 6 N HCl at 110°C for 24 h. Results expressed as mol/100 mol of amino acid.

	5	10
Tew B. J.	Asp-Ile-Val-Met-Thr-Gln-Ser-Pro-Leu-Ser-	
Tew Amyloid	Asp-Ile-Val-Met-Thr-Gln-Ser-Pro-Leu-Ser-	

	15	20
B. J.	Leu-Pro-Val-Thr-Pro-Gly-Glu-Pro-Ala-Ser-	
Amyloid	Leu-Pro-Val-Thr-Pro-Gly-Glu-Pro-Ala-Ser-	

	25	
B. J.	Ile-Ser-Cys-Arg-Ser-Ser-Gln	
Amyloid	Ile-Ser-Cys-[ ]-Ser-Ser-Glx	

FIGURE 3 Amino-terminal sequence of Tew amyloid protein compared with the sequence of Tew Bence Jones protein (Whitley, E. J., and F. W. Putnam, personal communication). Sequence was obtained with an automatic protein sequencer. Brackets [ ] indicate residue not identified.

fibril and Bence Jones proteins are identical in their amino-terminal portions.

The results of the acrylamide gel and peptide map studies suggested that the amyloid protein was an intact light polypeptide chain. Additional studies were performed to determine whether the carboxy-terminal tryptic tripeptide expected for κ-type light polypeptide chains could be isolated from the amyloid protein. Preparative tryptic peptide maps of the amyloid and Bence Jones proteins were prepared and sprayed lightly with ninhydrin to locate peptides in the area of the map where the C-terminal peptide should migrate (Fig. 2). As expected, only one peptide was found in this region (below and to the left of the arrow indicating direction of chromatography) and the compositions of the amyloid and Bence Jones peptides were compared with that expected for the κ-chain C-terminal peptide (Table II). These results indicate that both the amyloid fibril protein and the Bence Jones protein contain a peptide identical with that expected for the carboxy-terminus of a κ-light chain and provide further evidence that the Tew amyloid protein is an intact κ-chain.

DISCUSSION

The major constituent of the amyloid fibril protein isolated from the tissue of this patient with plasma cell

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TABLE II

Molar Ratios Relative to Glu

	κ-Chain expected	Tew Bence Jones obtained	Tew amyloid obtained
Gly	1	0.87	0.86
Glu	1	1.00	1.00
Cy SO₃H	1	1.34	1.17

Amino acid compositions of tryptic tripeptides eluted from Tew amyloid and Bence Jones maps, compared with expected composition for C-terminal tripeptide of κ-type light polypeptide chains.

Amyloid Fibril Protein Structure   1279

TABLE III
Summary of some Chemically Characterized Major Amyloid Fibril Proteins

Patient		Clinical reference	Organ analyzed	Amyloid fibril N-terminal sequence	Reference
5 (Ale)	1° Amyloidosis	(4, 5)	liver	κ-chain	(2)
4 (Art)	Amyloidosis with epidermolysis bullosa and tuberculosis	(4)	spleen	κ-chain	(2)
14 (Tew)	Amyloidosis with plasma cell dyscrasia	(8)	intestine	κ-chain	This paper
(LuA)	Isolated nodular pulmonary amyloidosis	(*)	lung	λ-chain	(6)
A-4	Amyloidosis with tuberculosis	(13)	liver	Arg-Ser-Phe-Phe-	(14)
2 (Med)	Amyloidosis with rheumatoid arthritis	(4)	spleen	Arg-Ser-Phe-Phe-	(15)
Paa	1° Amyloidosis	‡	thyroid	Ser-Phe-Phe	§
Pab	Amyloidosis with bronchiectasis	‡	thyroid	Ser-Phe-Phe	§

* Page, D. L., C. Isersky, M. Harada, and G. G. Glenner. 1972. Immunoglobulin origin of localized nodular pulmonary amyloidosis (18).
‡ Anders, R. Personal communication.
§ Glenner, G. G., R. Anders, and W. D. Terry. Unpublished data.

dyscrasia appears to be an intact κ-polypeptide chain identical with the Bence Jones protein isolated from the patient's urine. The evidence for identity is as follows: (a) The reduced and alkylated purified amyloid fibril protein gave acrylamide gel electrophoresis patterns identical with those obtained with the Bence Jones protein. (b) The sequence of the amino-terminal 27 amino acids was identical for both proteins. (c) Both proteins had a carboxy-terminal tripeptide (defined by the absence of lysine or arginine) of appropriate peptide map location and amino acid composition for the C-terminal peptide of a κ-chain. (d) Amino acid compositions were essentially identical and peptide maps of the two proteins were indistinguishable, indicating that no major insertions or deletions are present in the portion of the amyloid fibril protein molecule not directly sequenced. The data concerning the yield of protein extracted from amyloid tissue, as well as the yield of the N-terminal amino acids in the sequencer, indicate that the amyloid protein being sequenced is indeed the major protein constituent of the amyloid fibrils, and it seems reasonable to conclude, therefore, that the major protein constituent of the amyloid fibrils is the complete κ-Bence Jones protein that was present in the patient's circulation and urine.

Previous studies have shown that the amyloid fibril proteins from a case of primary amyloidosis (2, 4, 5) and a case of amyloidosis secondary to epidermolysis bullosa and pulmonary tuberculosis (2, 4) had amino acid sequences homologous with those of κ-chains (Table III). The amyloid protein from a patient with isolated nodular pulmonary amyloidosis was shown to have an amino-terminal tetrapeptide homologous with that of λ-chains (6, 18). The present work adds amyloid associated with plasma cell dyscrasia to the group of disease states with immunoglobulin proteins in the amyloid deposits.

The pathogenic significance of these results are obscure, but certain possibilities deserve consideration. As previously reported, the plasma cell dyscrasia and associated amyloidosis in this patient were preceded by many years of chronic colitis (8). It was further shown that fluorescein-labeled Tew Bence Jones protein had an unusual binding affinity for small intestine, which could be specifically blocked by pretreatment with the unlabeled Bence Jones protein. It was therefore suggested that the Tew Bence Jones protein might have been part of an autoantibody, i.e., the light chain of an anti-intestine antibody, produced in great excess as a consequence of the development of a plasma cell dyscrasia after long-term intestinal inflammatory disease. This implies that the deposition of the Bence Jones protein, at least initially, is a specific immunologic phenomenon. The continued accumulation of the Bence Jones would then be the proximate cause of the amyloidosis, perhaps due to a combination of immunologic and physicochemical properties.

Whereas the above speculations are consistent with the clinical and experimental data, there is no proof for this hypothesis. Alternative speculations can be generated and further experiments will be required to achieve an understanding of the pathogenesis of this disease.

The finding that the major protein component of certain amyloid deposits does not appear to be an immunoglobulin (13–17) is obviously important to any speculations concerning pathogenesis. It is possible that these amyloid fibril proteins of unknown origin are related to immunoglobulins and that they are: (a) a new variable region subgroup of either light or heavy chains, (b) a fragment of a constant region of a light or heavy chain that has not yet been sequenced, or (c) a portion of S-piece, J-piece or of some other immunoglobulin associated polypeptide chain that is as yet unsequenced. Alternatively, either of the two different types of amyloid

fibril protein may be deposited in tissue as the end process of two entirely different pathogenetic mechanisms. This seems unlikely, since one patient with amyloid fibrils of immunoglobulin type had the clinical picture of chronic disease that is stated to be more frequently associated with amyloid fibril protein of unknown origin (2, 4), and, conversely, the thyroid of at least one patient with the clinical picture of "primary" amyloidosis without known chronic disease contained amyloid fibril protein of unknown origin.[4] The overlapping clinical pictures asociated with tissue deposition of each type of amyloid fibril protein suggests that they both may result from similar pathogenic mechanisms.

The work presented here demonstrates that when a patient with plasma cell dyscrasia produces a monoclonal protein and develops amyloidosis, the major protein in the amyloid may be that monoclonal protein. It will be important to investigate other patients of this type to determine whether this is an invariable finding, or whether in some patients with this clinical picture, the "nonimmunoglobulin" form of amyloid fibril protein can predominate in the tissues.

ACKNOWLEDGMENTS

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