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Disclosures for Robert A. Kyle

None Related to the Presentation
History of Monoclonal Proteins

- 1838 Gerrit J. Mulder, Rotterdam
- Described “oxidized basic radical” in serum, egg albumin and gelatin
- 1838 Jöns J. Berzelius, Sweden (chemical symbols and formulae)
- Protein means “of the first rank or position”

Saturday, Nov 1st, 1845

Dear Dr. Jones: The tube contains urine of very high specific gravity. When boiled it becomes slightly opaque. On the addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear; but as it cools, assumes the consistence and appearance which you see. Heat reliquifies it. What is it?

Dr. T. Watson
Justus Von Liebig
1803-1873
Hydrated deutoxide of albumen

“I need hardly remark on the importance of seeking for this oxide of albumen in other cases of mollities ossium.”

H.B. Jones 1847
Henry Bence Jones

• No hyphen

• Hyphen added 50 years after his death by his son
Bence Jones Protein

- 1880 Fleischer – Used term “Bence Jones Protein”
- 1898 Bradshaw – No nocturnal change
- 1917 Jacobson – BJP in blood
- 1921 Walters – Protein in diet had no effect
Bence Jones Protein

1922
Bayne-Jones and Wilson

1956
Korngold and Lipari
Bence Jones Protein

Light chains of serum monoclonal protein in patient identical to Bence Jones protein in urine by:

- Same amino acid sequence
- Same molecular weight
- Same ultracentrifugal pattern
- Same thermal solubility

Medical Resident

- It is so easy when known
- Bored with explanation of light chains
- “Learned in freshman Biochemistry”
Bence Jones Protein (Free Light Chain)

• 1975 Light chains separated from serum by radioimmunoassay

Sölling K, Scan J Clin Lab Invest 1975; 35:407-12
Serum Protein

- 1928 Perlsweig – Duke University
- Hyperproteinemina in myeloma
Theodor Svedberg
1884-1971
Theodor Svedberg 1884-1971

- PhD University of Uppsala 1907
- Preparation of colloidal solutions of metals
- Size of colloidal particles determined by rate of settling
- Nobel Prize 1926
Theodor Svedberg

- Visiting Professor, U of Wisconsin-Madison, 1923
- Built first Ultracentrifuge
- Studied 2 cases of Waldenström’s Macroglobulinemia, 1944
Electrophoresis

Theodor Svedberg

• Separation of serum proteins by electric charge on gelatin 1925
Arne Tiselius
1902-1971
Electrophoresis

Arne Tiselius
1902-1971

- Chemistry – U. of Uppsala, 1921
- Research Assistant, 1925
- U tube for electrophoresis, 1926
- Moving boundary for electrophoresis utilizing refractive indices of proteins, 1930
Tiselius U-TUBE

Fig. 3. Electrophoresis U-tube assembled with electrode containers for reversible electrodes.

Diagram of a Tiselius electrophoresis apparatus.
Electrophoresis

Arne Tiselius

• Discovered 4 bands in horse serum, 1937 – albumin, α, β, γ

• Rejected by Biochemical Journal

• Published in Transactions of the Faraday Society
Electrophoresis of Serum

• 1939 Longsworth demonstrated a spike in 2 patients with multiple myeloma

• One technician, 1 day, 1 patient

• Cost, $5,000
Electrophoresis of Serum

- 1951, Kunkel and Tiselius – Introduction of filter paper electrophoresis
Arne Tiselius (left) and Henry Kunkel (right) in 1949-50, University of Uppsala. The photo was obtained from Arne Tiselius’ son Per Tiselius.
Electrophoresis

- 1955 (December) Bernard McKenzie
- Began serum protein electrophoresis at Mayo Clinic
Diagnostic Criteria for Electrophoretic Patterns of Serum and Urinary Proteins in Multiple Myeloma

Study of One Hundred and Sixty-five Multiple Myeloma Patients and of Seventy-seven Nonmyeloma Patients with Similar Electrophoretic Patterns


Much has been written about the electrophoretic patterns of serum and urinary proteins in multiple myeloma in recent years, but little has been said about borderline patterns or 'minor abnormalities.' Few analyses of "myeloma patterns" occurring in other disease processes can be found. With this in mind, we have attempted to define electrophoretic criteria for the diagnosis of multiple myeloma.

Background Data

Longsworth and associates, in 1939, reported the first serum electrophoretic patterns in multiple myeloma when they found a homogeneous peak in the beta region in two of three cases of myeloma. Then, in 1940, Kokwick found that four of five patients with multiple myeloma had increased gamma globulin, while the fifth had increased beta globulin as shown in serum electrophoretic studies. In 1949, Adams and associates presented 33 cases of myeloma in all of which the patterns were regarded as abnormalities. In 21 there were major abnormalities consisting of tall, narrow peaks ranging from beta to slower than gamma in electrical mobility, and in 8 there were minor, nondiagnostic abnormalities. Details of the remaining four cases were not described in that report.

In 1953, Reiner and Stern found that 71 of 91 multiple myeloma patients (78 per cent) had a major, tall, sharp abnormal peak in their serum electrophoretic patterns and that the remaining 20 had minor abnormalities; hence, none could be said to have had a completely normal serum electrophoretic pattern. The incidence of Renal Jones proteinuria was highest among patients with minor abnormalities.

Of 165 electrophoretic patterns of serum proteins in 165 patients with multiple myeloma, 126 were considered diagnostic of "myeloma proteins" because either the abnormal protein component in the pattern had a height-width ratio of 3:1 or greater, with the method used, or had a significant peak of height-width ratio of 3:1 or greater with an electrophoretic mobility faster than that of gamma globulin. By these criteria, 30 additional patterns were definitely abnormal, though not diagnostic, while only 9 were regarded as essentially normal. Thirty-seven of 62 urine electrophoretic patterns had a significant abnormal globulin component. No patient with multiple (disseminated) myeloma had a normal serum electrophoretic pattern in the absence of proteinuria. Only 15 of 6,031 serum electrophoretic patterns in nonmyeloma patients were indistinguishable from the typical pattern of multiple myeloma. These included macroglobulinemia, amyloidosis, and lymphoma.

Oserman and associates, in an excellent review in 1957, reported that 57 of 100 patients in the myeloma spectrum had an "abnormal spot" either in the serum or the urinary electrophoretic pattern. Forty-eight had both serum and urinary abnormalities, while 36 had a serum "spot" but no significant urinary abnormality. Sixty-one had an abnormal urinary protein peak, but 13 of these had a normal serum electrophoretic pattern. Data on the serum
Monoclonal Protein Height-Width Ratio

Gammopathy Concept

• Monoclonal – Malignant or potentially malignant

• Polyclonal – Reactive or inflammatory

J. Waldenstrom, Harvey Lectures 56:211, 1961
so easy it seemed
Once found, which
Yet unfound most
Would have thought
Impossible.

John Milton
Immunoelectrophoresis and Immunofixation

- 1953, Immunoelectrophoresis – Grabar & Williams
- 1964, Immunofixation – Wilson
- Mass Spectroscopy (MALDI)
Monoclonal Gammopathy

- Waldenstrom - “essential hypergammaglobulinemia”
- “Benign monoclonal gammopathy”
- 1978 Kyle - Monoclonal gammopathy of undetermined significance (MGUS)
“Benign” Monoclonal Gammopathy?

- **July 1964**
  - Low back pain
  - Hb 8.5 g/dL, γ-spike 3.9 g/dL
  - Compression fx, Lytic lesions
  - Bone marrow: plasma cells 23%
  - Diagnosis: Multiple Myeloma
  - RoRx, Cyclophosphamide

- **March 1965**
  - Died

“Benign” Monoclonal Gammopathy?

Mrs. A., 49 yo wf

- April 1945
- Fatigue
- Hb 12.3 g/dL, sed rate 118
- Alb/glob: 4.9 g/dL/4.3/dL

"Benign" Monoclonal Gammopathy?

Mrs. A., 49 yo wf (cont)

- Bone x-rays: Negative
- Bone marrow: plasma cells 3.6%
- Rx: 0

“Benign” Monoclonal Gammopathy?

May 1958: Doing well

- Hb 11.9 g/dL, sed rate 120:
  \( \gamma \)-spike 2.9 g/dL
- Bone marrow: plasma cells 4.5%
- Rx: 0

“It is not safe to assume that these patients have a benign condition even after years of observation.”
