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Essential Paraproteinæmia

Essential paraproteinæmia was a term used by Waldenström (1952) to describe paraproteinæmia in patients without frank malignancy and the subject has been reviewed recently by Hällén (1966) and Hobbs (1967). In most of the series cited the essential group represented 10% of all paraproteinæmias although they represented 23% of Hobbs's own series. The 69 cases listed in Table 1 represent 30% of all paraproteinæmias referred to this laboratory.

The cases are grouped according to the site of the associated disease, with gut and liver diseases accounting for nearly half of the cases. Distribution of the paraproteins among the immune globulin types (25% γA, 67% γG, 8% γM) is similar to that seen in myelomatosis and Waldenström's macroglobulinæmia but some groups show a marked divergence. Thus there were no γA paraproteins associated with heart disease, whilst 40% of the paraproteins associated with collagen diseases were γA globulins.

There was no association between paraprotein type, site of disease and the immune-globulin changes usually seen in the associated disease. Thus γG paraproteins predominate both in the gastrointestinal group, although gut is rich in tissue producing γA globulins, and in Laennec's cirrhosis where a marked increase in γA globulin is common.

Four criteria are generally used to identify myeloma proteins as distinct from essential paraproteins:

(1) *The presence of Bence-Jones proteinuria:* None of these 69 cases had Bence-Jones proteins.
(2) *Suppression of other immune-globulin levels:* In essential paraproteinæmia the immune-globulin pattern resembles that of the associated disease and increased levels of all immune-globulins are common. Rarely an immune-paresis occurs, the long-standing PUO in Table 1 being such a case.
(3) *Paraprotein levels in excess of 1 g/100 ml for γA or γM or 2 g/100 ml for γG globulin:* This is the least valuable test since high paraprotein values are frequently associated with the collagen diseases. Juvenile cirrhosis, aplastic anæmia, lichen planus and the long-standing PUO also gave levels above these limits.

Table 1
Analysis of 69 cases of essential paraproteinæmia

Disease type	*Diagnosis of associated disease*	*Immune globulin type* γA	γG	γM
Gastrointestinal disease (11 cases)	Ulcerative colitis	1	4	–
	Steatorrhea	–	3	–
	Pancreatic steatorrhea	–	1	–
	Diarrhœa	–	1	–
	Massive gut bleed	1	–	–
Liver disease (20 cases)	Cirrhosis:			
	Lænnec's	2	11	–
	Biliary	1	–	–
	Juvenile	–	1	–
	Hepatomegaly	1	1	–
	Undefined jaundice	–	1	–
	Acute infective hepatitis	–	–	2
Heart disease (6 cases)	Congestive cardiac failure	–	3	1
	Aortic transplant	–	1	–
	Aortic stenosis	–	1	–
Reticulo-endothelial system (12 cases)	Henoch-Schönlein purpura	2	5	1
	Amyloid	1	1	–
	Aplastic anæmia	1	–	–
	Myeloproliferation	–	1	–
Collagen diseases (10 cases)	Ankylosing spondylitis	1	2	–
	Rheumatoid arthritis	2	–	–
	Disseminated lupus erythematosus	–	2	–
	Sarcoid	–	2	–
	Polyarteritis	1	–	–
Other diseases (10 cases)	Optic atrophy; cerebral vascular accident; lichen planus	3	–	–
	Tuberculosis; hypertension; pernicious anæmia; Addison's disease; long-standing PUO	–	5	–
	Acute glomerular nephritis	–	–	2

(4) *A rapid increase in paraprotein concentration:* Pancreatic steatorrhea gave the most marked increase, a doubling of paraprotein concentration in 3 years. In many cases the level remained constant for 3–6 years. In one of our cases of Henoch-Schönlein purpura (Birch *et al.* 1964) the paraprotein disappeared after removal of a benign thymoma and never recurred.

Paraproteinæmia is also often associated with old age and Hällén reported it in 3% of all subjects over 70 years of age compared with Hobbs's findings of 0·8% in a hospital population and no cases among 10,000 consecutive blood donors examined personally (Cooke *et al.* 1961). However, only 53% of the present cases were aged 60 years or over compared with 73% of Hällén's series so that age alone is not a valid criterion.

In the diagnosis of essential paraproteinæmia the absence of Bence-Jones protein and a steady paraprotein concentration are thus the most valuable criteria.

Detailed protein studies, of great importance in myelomatosis, have rarely been applied to essential paraproteinæmia. Mårtensson (1961) included 4 cases in his studies of Gm groups in myelomatosis and decided that in each case the protein was the product of a single gene. He had difficulty in allowing for the normal background γG globulin present, a problem that has hampered my own studies on the light-chain heterogeneity of paraproteins. In contrast to the myeloma proteins it is unusual to demonstrate a single light chain by starch gel electrophoresis of reduced and alkylated paraprotein. Only when such criteria can be applied to essential paraproteins will it be possible to decide if they are truly monoclonal.

Acknowledgments: I am grateful to Dr Eunice Lockey, National Heart Hospital, Dr Hilary Berry, Redhill Hospital, Dr J Swale, Charing Cross Hospital, and the clinical staff of Westminster Hospital for sera and clinical histories; to Dr Margaret Apsey, Miss P Gunewardena and Miss W Woolley for performing many of the analyses on which this work is based; to Professor N F Maclagan for his support; and to the British Empire Campaign for Cancer Research for generous grants towards equipment and expenses.

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Transient Paraproteins

By 'transient paraprotein' is meant a monoclonal protein which has suddenly appeared, increased quite rapidly to a peak value, and rapidly declined spontaneously, usually disappearing within weeks or months.

A review of the literature reveals 31 claimed cases (Table 1). The monoclonal nature of the paraprotein was proved by immunoelectrophoresis in Cases 1–24 only: Cases 25–31 are therefore considered less satisfactory. They showed a wide age range (2 months to 80 years when the paraprotein was first noted), but 22 of the 31 (70%) were 50 years or more. There were 14 males and 17 females.

Twenty patients presented with conditions where an immunoglobulin response of some sort might be expected; of these, most had infective illnesses, but there were other conditions, e.g. rheumatoid arthritis, hepatic cirrhosis, and sensitivity to cold. In contrast, there was a case of hypogammaglobulinæmia, and 2 cases of the Wiskott-Aldrich syndrome, a condition usually associated with defective immunoglobulin synthesis. In the latter two conditions, it is possible that only a single clone of cells retained the ability to respond to an antigenic stimulus.

In 2 cases associated with epithelial tumours (Cases 25, 26) proof of the monoclonal nature of the abnormal protein was unsatisfactory. In Cases 19–22 the paraprotein disappeared during treatment which could have suppressed any associated reticuloendothelial tumour, but it apparently disappeared spontaneously in Case 24, a patient with Waldenström's macroglobulinæmia.

Several patients had a 'remission' while on corticosteroid therapy, but as Hällén (1966) remarks: 'The course in those cases treated with corticosteroids or ACTH lends no certain support to the assumption that the therapy had caused the M-component to disappear.'

Because of multiple drug treatment, it is difficult to prove an association between therapy and paraprotein. Osserman (1967) has suggested that the paraproteinæmia may result from a sensitivity reaction to sulphonamide (Case 9), but he has been unable to prove this.

The time between discovery and disappearance of paraprotein varied from 1 to 45 months. However, in nearly all patients the time at which the paraprotein appeared in the serum was not known, only the time of discovery. Also, in most cases, it had disappeared by the time of a second electrophoresis, so the actual time of disappearance was also unknown.

The paraprotein level was 1 g/100 ml or less in 22 of 27 levels recorded. However, some authors reported only a single value, while others gave a peak level.

Gamma-globulin levels showed no consistent pattern either when the paraprotein was present, or subsequent to its disappearance.

Of seven reports mentioning examination of urine for Bence-Jones protein, 3 were positive (2 Type K, the other untyped). In one of these it disappeared; in the other 2 cases, we were not told.