

Hobbs J R. Paraproteins, benign or malignant? *Brit. Med. J.* 3:699-704, 1967.
[Postgraduate Medical School, London, England]

Improved protein assay methods applied to 223 well-defined malignant conditions and 70 established benign states were used to establish predictive criteria for malignant or benign paraproteins, with clinical follow-up for up to eight years. Biochemical measurements were used to estimate that there would be about 1 kg of tumour cells in a 70 kg patient with the average presentation of myeloma, and this agreed with the independent parameter of counting myeloma cells in bone marrow samples. Measurements of the paraprotein tumour markers permitted us to estimate the tumour mass, follow the natural history and progress of the disease, and predict a benign or malignant outcome. [The SC¹⁰ indicates that this paper has been cited in over 165 publications.]

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Methodology in clinical chemistry was undergoing "the purge" of quality control, and my new chief, Ian Wootton, persuaded me to thoroughly overhaul the protein assay methods of the department. Automatic samplers then in use did not allow for the increased viscosity of paraprotein-containing sera. Only reliable manual Biuret estimations gave duplicates agreeing ± 1 percent. I produced 99 percent pure samples of immunoglobulins G, A, and M to standardise the Mancini method, with parallelism between assays for normal immunoglobulins but not for paraproteins, which therefore had to be measured in some other way.

Joachim Kohn's new trick of "clearing" the dried cellulose acetate in oil enabled transmission scanning after electrophoresis. Amido-black 6B gave near-uniform dye uptake provided only 0.25 μ l of sample was applied across 1 cm when the paraprotein band uptake could be reproduced within 2 percent and related to the total protein of the sample.

Previous assay methods for Bence-Jones proteins' were discredited and a new definition based on "monoclonality" was introduced, together with a new approach to urine concentration and electrophoresis. So at last the first tumour marker of man (1845)² could be carefully measured and monitored.

I was invited to undertake studies for the MRC Working Party on Leukaemia in Adults (then chaired by L. Witts) during the myeloma trials. The stimulating meetings (then at Bruges) on "Protides of Biological Fluids" kept me abreast of protein turnover studies and of the paraprotein work of others such as C.B. Laurell, J. Waldenström, J. Heremans, J. Fahey, M. Potter, E. Osserman, and others.

Another influence was an early introduction to tissue culture and cellular dynamics by J.G. Pulvertaft at Westminster Medical School. Harold Hewitt discussed induction periods from a model of mouse leukaemia passaged with a single cell. During my London MD thesis (1963) on radioiodine in thyroid disease, carcinogenesis was studied using volume measurements from serial chest X rays of pulmonary metastases of thyroid cancer. This was the origin of the concept of near exponential growth, at least in the surviving, then-untreated, measurable tumour cells.

Looking back, the paper does seem to have been the first serious attempt to produce tumour-marker measurements and relate them to evolving disease in man. Myeloma had the advantage that it grows in a lake of blood without necrosis. The cytotoxic drugs (cyclophosphamide and melphalan) had been previously available for up to eight years, but their early use had hardly affected the median survival of eight months from diagnosis. Tumour-marker guidance achieved median survivals of 24 months—in those days a huge improvement. The paper also provided the first criteria to predict a benign or malignant outcome.

Clearly, somewhere, the 100 percent "growth fraction" of the original clonal cell declines to the average of 4 percent or so found in clinical myelomatosis cells, permitting Gompertzian speculations on growth curves. Where this happens is still unknown and unmeasured. In clinical practice or in mouse tumour lines, by the time early untreated paraproteins are found, the growth fraction is mostly low and constant, so that measured growth approximates exponential growth (or else the Gompertzian coefficient is so small that it doesn't matter).³ The final flattening of the growth curve (late or relapsed myelomatosis) and the deterioration of the host are so multifactorial they defy statistical analysis.

1. Hobbs J R. The detection of Bence-Jones proteins. *Biochemical J.* 99:15P, 1966.
2. Clump J R. Some aspects of the first recorded case of multiple myeloma. *Lancet* 2:1354-6, 1967.
3. Hobbs J R. Plasma cell tumours of man and mouse. (Peeters H, ed.) *Protides of biological fluids*. Oxford: Pergamon, 1980. p. 3-13.