Plasma Cell Dyscrasias: A Current Perspective

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In the past 25 years there have been remarkable advances in our understanding of many of the basic biochemical and immuno-nological aspects of multiple myeloma and related plasma cell dyscrasias. Detailed studies of myeloma proteins and their poly-peptide subunits were, in great measure, responsible for elucidating the structure of normal antibodies. More recently, comparable analyses of the DNA sequences encoding immunoglobulins are providing insight into the organization and genetic control of antibody synthesis and secretion. It would be difficult to identify another area of medicine in which the integration of basic science with clinical medicine has been as productive as in the field of myeloma. Having made this statement, however, it is necessary to ask whether basic science or clinical medicine has profitted more from this enterprise. At the moment, it would seem that basic science is 'ahead'. Thus, an enormous body of information has been assembled concerning the chemistry and structure, including the three-dimensional structure of monoclonal immunoglobulins and antibodies and their combining sites, organization of immunoglobulin genes, identification and function of specific markers on lymphocytes, i.e. membrane immunoglobulins, Ia, idiotypic determinants, receptors, etc. It

must be asked, however, whether any or all of this information has resulted in advances in our clinical capabilities. For the moment, the answer can only be a qualified yes. Thus, electrophoresis and immunoelectrophoresis greatly improved diagnostic skills and our ability to monitor the course of disease and effects of chemotherapy. Introduction of the alkylating agents, melphalan and cyclophosphamide, 20 years ago represented a major advance in therapy and resulted in an unequivocal increase in life span for patients with myeloma. However, in most clinics throughout the world, the median survival for these patients is still only 3–4 years from the time of diagnosis. Other chemotherapeutic agents, particularly adriamycin and the nitrosoureas have proven of some value in patients resistant to melphalan and/or cyclophosphamide, but this is usually a relatively short-term effect. Obviously, we must do much better.

25 years ago, myeloma was considered a relatively rare disease and, indeed, it probably was. More recently, however, the incidence of myeloma has unequivocally increased such that it is now in the United States, the most common hematological malignancy in blacks and is equal in frequency to Hodgkin's disease among whites [1]. An absolute increase in the incidence of mye-

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loma has apparently occurred and not just an improvement in diagnosis. Are there environmental or dietary factors? Efforts to identify these factors have been unrewarding and a great deal more work is needed in this area.

In my opinion, basic science is still obligated to be of greater assistance to clinical myeloma. I believe that one area in which this will occur is in the delineation of the antibody specificity of all myeloma proteins. In 1964, Waldenström et al. [2] stated 'Our understanding of the pathology in myeloma and in similar conditions with an increase in so-called M components would be greatly advanced if we could decide whether this increased globulin is chemically abnormal or whether it is one of the normally occurring gamma globulins and is increased only in quantity.' At that time, most investigators regarded myeloma proteins as 'abnormal' products of neoplastic plasma cells. In the interval, however, a wealth of information has emerged which implies the opposite, namely, that myeloma proteins are, in fact, functional antibodies to specific antigens [3–5]. The types of antigens which have been identified thus far include polysaccharides, lipids, proteins and small ligands such as riboflavin, vitamin K₁₇ and dinitrophenol and its derivatives. Many of these antigens are autogeneous, e.g. the *Ii* antigens related to blood group substances, coagulation factors, immunoglobulins per se (rheumatoid factor). Others appear to be exogenous and primarily related to bacterial sources, e.g. streptolysin, *Klebsiella* antigens and phosphorylcholine. A common feature of these putative antigens is their persistence, either as a component of self or of commensal bacterial flora. It remains to be determined whether these putative antigens are responsible for initiating the dyscrasias in individual cases and, if so, what specific defects in the normal controlling mechanisms allow the process to progress to overt myeloma. Finally, we must recognize that antigens have only been identified for a very small percentage of monoclonal proteins and these are mostly IgM macroglobulins. Since monoclonal IgG and IgA proteins are incapable of forming a precipitating lattice with their antigens, simple screening procedures are ineffective for the detection of their interactions. New and innovative approaches will therefore be necessary for the identification of the specificities of these proteins.

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