Myelomatosis
Fundamentals and Clinical Features

I. Snapper and A. Kahn

With 90 figures and 24 tables


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Foreword

In the era of so-called 'modern medicine', there has possibly been no disease which has been the subject of greater interest and more fruitful investigation than multiple myeloma, and no single investigator who has contributed more to this subject than Dr. Snapper. Seventeen years have now elapsed since publication of the now-classic treatise Multiple Myeloma by I. Snapper, L.B. Turner and H.L. Moscovitz (Grune and Stratton, New York, 1953). This work represented a thoroughly scholarly review of the then-available clinical and biochemical information on myeloma and an equally comprehensive analysis of Dr. Snapper's personal series of 97 cases.

To this day there is no better description of the diverse and complex manifestations of the disease, exquisitely analyzed by one of the world's truly superb physician-investigators. Thus, what to many at the time was still regarded as a rare and usually dismal bone cancer, was recognized by Dr. Snapper to be a particularly challenging 'metabolic' disease with broad implications in the areas of pathophysiology, biochemistry and immunology. Clearly, the impressive wealth of information which has been added in the intervening 17 years to our knowledge of myeloma proteins as well as clinical myeloma and related diseases has amply affirmed Dr. Snapper's original convictions.

As detailed in this present volume, extensive studies of myeloma proteins have provided much of our present understanding of the composition and structure of normal immunoglobulins. Indeed, there is increasing evidence that certain myeloma proteins may in fact be functional antibodies produced in great excess as a consequence of the excessive proliferation of plasma cells.

With regard to the clinical aspects of myeloma, the past several years have also witnessed impressive progress, not only with respect to improved diagnostic methods but also more effective chemotherapy and increased survival.

Foreword XII

Thus, it is greatly welcomed to have the subject of myeloma and myeloma proteins surveyed and re-appraised by a physician and clinical-investigator non-pareil, Dr. I. Snapper.

December, 1970
Elliott F. Osserman, M.D.
American Cancer Society Research
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Henry Bence Jones

Introduction
The complicated disease nowadays known as multiple myeloma or myelomatosis first came to the attention of the medical profession when MacIntyre and Bence Jones in 1845 discovered a unique protein in the urine of a patient suffering from an unknown ailment. Before the pathogenesis of the disease was well understood, it was necessary for several generations of investigators to formulate and test an impressive variety of theories. The diagnosis made at the autopsy of the first patient in 1846 was mollities ossium, 'softening of the bones'. For the next four decades the few physicians interested in this syndrome were unable to differentiate the new disease from osteomalacia. In 1885, however, Kahler correctly concluded that the presence of the unusual protein in the urine excluded the possibility of osteomalacia and strongly militated in favor of a myeloma, the pathology of which had in the meantime been described by Rustizky.

Physicians working on the problems of myelomatosis were for a long time interested mainly in the skeletal changes, visualized on roentgenograms. Soon it became evident that roentgenologically this disease was characterized by a generalized 'decalcification' of the skeleton complicated by the presence of round, sharply defined, punched out osteolytic areas. At the same time no manifestations of new formation of bone could be found. Interesting as these bone lesions are, there can be no doubt that in a significant number of myelomatosis patients no clear-cut roentgenologic skeletal changes can be demonstrated.

As long as the histologic analysis of the skeleton of these patients was limited to the study of bone biopsies, only the profuse proliferation of abnormal bone marrow elements could be observed. The ancestry of the proliferating cells had yet to be traced. When in 1929 bone marrow punctures were introduced in the practice of medicine, the proliferation of immature, probably malignant plasma cells in the diseased bone marrow became the all-important feature of the disease. Anemia being one of the most common manifestations of myeloma, the hematologists' practice of performing bone marrow punctures in every anemic patient permits many utterly unsuspected cases of myelomatosis to be recognized by serendipity, hereby greatly increasing the number of cases of myeloma diagnosed during life.

In the course of the years interest of many physicians had turned to other clinical aspects of the disease. The published reports on the subject of myeloma dealt with such aspects as:

1. anemia, thrombocytopenia, coagulation disorders, and other hematologic dyscrasias;
2. connection between myeloma
and plasma cell leukemia;
(3) very high sedimentation of the red cells;
(4) uremia - usually due to renal damage caused by Bence Jones proteinuria;
(5) hypercalcemia and hypercalciuria - in the absence of an increased alkaline phosphatase of the serum;
(6) Raynaud's syndrome - usually due to cryoglobulinemia;
(7) decreased resistance against tuberculosis, fungus diseases and other infections, - pneumonia and pyelonephritis being the most frequent manifestations of bacterial invasions;
(8) paramyloidosis - mainly localized in musculature and mesenchymatous tissues;
(9) neurological complications - often due to hyperviscosity of serum and hypercalcemia;
(10) relationship between generalized myelomatosis and solitary intraosseous or extramedullary plasmacytomas;
(11) connections between myelomatosis and Waldenstrom's macroglobulinemia;
(12) different modalities of heavy chain disease.

Notwithstanding the many different serious manifestations of myelomatosis, many patients suffering from this disease are walking around considering themselves to be completely healthy individuals. Patients may have none of the symptoms or signs of myelomatosis although their entire bone marrow is replaced by rapidly growing myeloma cells.

It soon became evident that the changes of the protein metabolism characteristic for myelomatosis are of paramount importance for the pathogenesis, diagnosis and prognosis of the disease. Researchers were obliged to become experts in immunochemistry, in order to be able to grasp the significance of many of the intricacies of the myelomatous proteins. Better understanding of these complicated problems has in turn clarified many of the chameleonic symptoms and signs of this disease.

For myelomatosis there is still no cure, but a faint ray of hope may now be visible on the horizon.

The circle has closed. In the first myelomatosis patient the disease of the skeleton was not recognized during life but a hitherto unknown protein had been discovered in the urine. We have now returned to the study of the abnormal myeloma proteins though with more sophisticated techniques.

In our choice of a sequence of chapters for this monograph we have been guided by the triad of examinations essential for the diagnosis, prognosis, and treatment of myelomatosis, i.e. bone marrow puncture, serum electrophoresis, and search for Bence Jones protein. Therefore, after a short historical
review, the multifaceted subject of myelomatosis is approached by preliminary chapters on: histology of bone marrow; immunoglobulins; and investigation of structure and metabolism of Bence Jones protein. Since certain other fundamental problems and laboratory methods could not be ignored, the discussion of clinical aspects of the disease was tackled last.