the major prolongation is in the G1 phase of the cell cycle. When nutritional limitations on growth are overcome evidence is obtained that crowding and contact inhibition as well as soluble metabolic factors may contribute to the limitations on proliferation.

The lymphoid and plasma cells in culture provide an interesting, though not completely analogous, model for studies of cell proliferation in vivo. The stationary culture shift to prolonged G1 phase, like a comparable event in vivo, should make cells resistant to chemotherapeutic agents that act primarily on DNA synthesis (S phase events). Mechanisms for affecting G1 cells or bringing arrested cells out of G1 are beginning to be explored.

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Immunoglobulin Synthesis and Tumour Cell Number and the Natural History of Multiple Myeloma

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Our recent studies of the synthesis, secretion, and metabolism of monoclonal immunoglobulins suggest that such observations may explain some of the features of multiple myeloma and related disorders. Essential for these studies was the development of radioimmunoassays capable of measuring nanogramme amounts of immunoglobulins produced by a few cells obtained freshly from the patient's bone marrow. Serial studies showed that for a given patient the average secretion rate of myeloma protein per myeloma cell may remain fixed for at least several years during the clinical course (both before and during chemotherapy).

So far over 40 patients with monoclonal IgG, IgA, IgM, and K or L secretion have been studied. Cellular immunoglobulin secretion rates were found to range from 12,500 to 87,500 molecules per minute (5 to 35 pg per day per plasma cell; average 12). If the measured or calculated total body synthesis rate for the patient's monoclonal protein (M-component) is divided by the average cellular rate, the resultant gives the total number of myeloma cells in the body. Our initial measurements of IgG myeloma showed that patients who can be clinically diagnosed as having myeloma have from 0.3 to somewhat over 3.0×10^{12} myeloma cells (about 3 kg) in the body. Similar quantities of tumour were present in monoclonal malignancies of other immunoglobulin types. Minor M-components generally cannot be detected by electrophoresis unless the tumour mass is at least 40 g.

These studies also indicated that even patients with "benign monoclonal gammopathies" usually have over 100 g of the progeny of a single plasma cell clone in the body. In IgG myeloma the degree of skeletal involvement correlated significantly with the total number of tumour cells in the body. Bence Jones proteinuria, hypercalcemia, and short survival were also much more frequent in patients with over 2.0×10^{12} tumour cells. The variation in serum concentration of the M-component in different patients with similar numbers of myeloma cells is a result of the variation in the secretory rate of the myeloma clones in these patients. During the clinical course little more than four doublings of tumour cell number occur from the time of "early" diagnosis until death with far advanced bone disease. The relation of the number of tumour cells to the natural history of disease and to the effects of treatment can be assessed by

relating the total number of tumour cells in patients with early and advanced disease with their average life expectancy. Similar estimations can also be made by measuring the rate of change of the total body synthetic rate of M-component in patients who are untreated, those who are treated, and those who relapse during treatment.

If clonal doubling occurred at a constant exponential rate from its initiation one would calculate that the tumour had been present for over 16 years before clinical diagnosis. Though the concept of a simple exponential growth mode is attractive—and superficially might seem likely from evaluation of electrophoretic patterns—this mode of growth is rarely observed in tumour in animals, including various plasmacytomas, for in these growth slows increasingly as the tumour enlarges. This phenomenon can be described with a Gompertzian growth equation, which contains terms not only for the growth rate at any given time (A), which is a function of the number of tumour cells, but also a constant (a) that sets the degree of slowing of tumour growth.

Growth of Myeloma in Man

To define the actual mode of growth of myeloma in man we have done a detailed study using frequent electrophoretic, plasma volume, and tumour-cell number determinations. Together with Dr. Peter Sullivan we have recently designed very precise computer programmes which can indicate whether growth of myeloma is exponential or Gompertzian. These new techniques have shown already that in man myeloma does indeed grow in Gompertzian fashion and that the exponential models grossly overestimate the duration of the disease. Though a tremendous "iceberg" of tumour cell proliferation occurs asymptotically before diagnosis, this growth appears to occur in under five years in the average patient. Possibly "benign monoclonal gammopathies" also grow rapidly at first, with retardation in the growth rate as the clone enlarges.

These studies have also been useful for analysing the effects of treatment of myelomatosis. Patients who have good responses to treatment generally have reductions of about two logs in the number of myeloma cells in the body. Interestingly, the mode of regression of the tumour during treatment with melphalan, alone or combined with prednisone, may also be described with the Gompertz equation. Using this equation we have predicted successfully the eventual plateau level of tumour in the body from a series of measurements made during the initial six to eight weeks of treatment, even though the plateau might not be reached for more than six to eight months. Such useful predictive techniques seem likely to bring about further improvement in the treatment of multiple myeloma.

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Natural History of Monoclonal Immunoglobulins

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In this contribution we discuss the fate of monoclonal immunoglobulin spikes detected in the absence of overt myeloma or Waldenström's macroglobulinaemia. Monoclonal immunoglobulins may occur transiently in the serum, disappearing without treatment. In recent years we have seen nine such