Multiple Myeloma

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The most striking feature of the distribution of multiple myeloma is the difference in its incidence in different races. Figure 1 shows the age-specific incidence of multiple myeloma in the San Francisco Bay area and illustrates the relatively high incidence in elderly blacks, the Chinese showing a notably lower incidence.

International comparisons of the incidence of multiple myeloma are difficult because diagnosis depends upon sophisticated techniques that are not universally available, and diagnostic criteria differ. The rarity of multiple myeloma in Ibadan, Nigeria (Edington, 1978) may be due to this or because shorter life expectancy reduces the population at risk. The low incidence reported in Japan (Waterhouse et al., 1976) may be a reflection of the same racial factors seen in San Francisco, but it is clear that their diagnostic criteria differ from those of the USA. In the UK there is an unexplained excess of myeloma in north-east Scotland (Dawson and Ogston, 1973). The practical implication of these findings is that immigrants from the West Indies and Africa will probably have a higher incidence of myeloma than British whites.

Apart from confirming the genetic contribution to the aetiology of myeloma, epidemiology has contributed little to our understanding of the cause of the disease. It has been suggested that the high incidence of myeloma in north-east Scotland could be associated with a high background level of radiation but, in survivors of Hiroshima and Nagasaki exposed to more than 100 rads, only one case of multiple myeloma was observed (Ichimaru and Ichimaru, 1975). This conclusion could, however, be criticised on the grounds that the population is less susceptible to myeloma than Caucasians and the latent period between exposure and development of myeloma may be more than the 20-year observation period.

The possible importance of oncogenic viruses in the production of multiple myeloma and its animal model, the mouse plasmacytoma, is under investigation. While RNA viruses are observed in mouse plasmacytomas (Watson et al., 1970) demonstration of a viral factor in man has extended only as far as showing a reverse transcriptase (characteristic of RNA viruses) in peripheral blood cells of myeloma patients (Sawada et al., 1977). The high incidence of myeloma among salespeople has been construed as evidence of an infective factor in multiple myeloma (Williams et al., 1977) but studies in medical personnel do not show the high incidence that would be expected if an infective factor was involved.

The demonstration that the paraproteins found in multiple myeloma have antigenic specificity (Lancet, 1978) has stimulated the search for cases in which the exposure to a particular antigen has been associated with the development of multiple myeloma whose paraprotein
reacts with the original antigen. This has been shown for only a handful of patients, one case being associated with chronic streptococcal infection (Kalliomaki et al., 1978) and another being associated with injection of horse serum 30 years before the development of the disease (Seligmans et al., 1973). In the mouse, it is certainly true that antigenic exposure is required for the development of a plasmacytoma, since germ-free mice do not develop the disease (McIntrye and Princler, 1969). Plasmacytomas in mice only develop after non-specific stimulation of the immune system by, for example, mineral oil (Potter and Boyce, 1962). It is likely that in both mouse and human the selection of a malignant clone takes place randomly, the choice of clone being limited to the individual's previous exposure. If a virus acts as a transforming agent, it is possible that some virus released from cells could act as a hapten with antigens, the hapten-antigen complex being recognised by virus receptors on the plasma cell clone.

**Cellular Immunology**

Although the bone lesions in multiple myeloma attract attention as the site of pain and of immunoglobulin production, they are only one facet of a generalised defect of the immune system.

The most significant finding has been the demonstration of a clone of lymphocytes in the peripheral blood of myeloma patients (Mellstedt et al., 1974). Their surface immunoglobulin is identical with the paraprotein being produced and their numbers mirror the state of the disease, falling in parallel with paraprotein levels during partial remission. Most workers find that the clone of lymphocytes is of B ('bursa' processed) lymphocytes, which is consistent with the idea that myeloma is due to a malignant clone of B cells (Salmon and Seligmans, 1974).

Very little information is available about the lymphocytes populating the lymph nodes and spleen in myeloma, but the immune defect seen in myeloma must indicate that these organs are not functioning normally. Turesson (1978) looked at lymph nodes and spleen from six patients with multiple myeloma at autopsy or splenectomy and found more than 90 per cent of the cells were of the same immunoglobulin class as the paraprotein being produced.

A model of the mechanism underlying myeloma can be built on this information (Fig. 2). Stem cells from the bone marrow may supply precursors to a recirculating pool of monoclonal lymphocytes whose numbers are maintained and increased by the generation of cells within the germinal centres of lymph nodes. This implies that the pathological clone is using the normal route of recirculation through the small blood vessels supplying lymph nodes (Ford and Gowans, 1969). Seeding of the lymphocyte clone back to the bone marrow results in the development of lytic lesions only where the local microenvironment is suitable, for instance where lymphocytes can co-operate with macrophages or T cells.

Some evidence that has accumulated suggests that the lytic bone lesion consists of an indolent cell population whose capacity for cell division and turnover is limited (Salmon and Durie, 1977; Drewinko and Alexanian, 1977). This is at variance with clinical experience, in which bone destruction can proceed at an alarming rate, and in the finding of a rapid fall in paraprotein level after the first cycle of chemotherapy (1.7 months median halving time, range 0.3 to 9.9 months, Alexanian et al., 1977c). These findings suggest that the data on cell turnover in myeloma should be re-examined.

It has been found that myeloma plasma cells label at a very low rate of 1 to 2 per cent after exposure to tritiated thymidine (Drewinko and Alexanian, 1977). This is not surprising, as they are normally end-cells that have become highly differentiated and have lost their capacity for cell division. Study of plasma cell turnover in antigen-stimulated lymph nodes has shown that the majority live a short life without active division (Miller, 1974). Drewinko and Alexanian (1977) calculated that there must be a very high rate of cell loss in myeloma, which may be due to maturation and senescence of cells. Thus, they calculated that the predicted cell doubling time of the tumour cell mass in two patients was 42 and 17 days, whereas the observed doubling time was 224 and 33 days respectively; this discrepancy can be resolved if it is accepted that there is a high rate of cell loss.

High rates of cell turnover in a tumour are difficult to reconcile with low labelling indices for plasma cells unless it is accepted that a precursor cell is contributing to the tumour mass. The demonstration by Mellstedt et al. (1977) that the lymphocytes in the bone marrow of myeloma patients show a higher labelling index than the plasma cells suggests that the small lymphocyte is the precursor cell. The real difficulty of identifying cells in mitosis makes this study particularly difficult.

If the suggested transformation and division of lymphocytes is taking place, this would explain the rapid fall in tumour cell mass occurring after the first course of
chemotherapy, since cell loss might continue while the input of new precursor cells into the tumour is reduced. It also raises the question of the morphology of the cell that makes the major contribution to the mass or paraprotein. There is some evidence to suggest that the bulk of immunoglobulin is produced before the mature plasma cell stage is reached.

In summary, it is now realised that the whole lymphoid system is deranged in multiple myeloma. Seeding of stem cells to the bone marrow probably causes the formation of osteolytic lesions which, although growing slowly, consist of cells that have a limited life-span and are continuously produced and destroyed.

**Diagnosis**

In advanced cases the diagnosis of multiple myeloma is easy, based on the demonstration of a combination of marrow plasmacytosis, paraprotein and lytic bone lesions (Durie and Salmon, 1977). It could be suggested that by the time most patients present it is already too late since bone destruction and renal failure are irreversible. Diagnosis at earlier stages is much more difficult and can only be made by constantly maintaining a high index of suspicion.

The clinical features with which patients usually present are back pain, weakness, and infection. Such patients may present to the physician or orthopaedic surgeon. Of 259 patients over the age of 50 presenting to an orthopaedic surgeon with low back pain, 5 per cent had secondary malignancy, including multiple myeloma (Fernbach et al., 1976). It was considered that the use of serum calcium, ESR and alkaline phosphatase might be adequate as a screening test for malignancy in this group, but these would probably miss a small proportion of myeloma patients in whom by chance the tests were normal (Blattel, 1977; Fruzanski, 1977). The addition of serum and urinary electrophoresis to the above three tests would be more satisfactory, although more expensive.

The fact that multiple myeloma is now treatable makes it worthwhile being aware of the less common presentations of myeloma, shown in Table 1.

| Table 1. Some Less Common Presentations of Multiple Myeloma. |
|-------------------------------------------------------------|
| Epistaxis | Hyperviscosity syndrome (Preston et al., 1978) |
| Gastrointestinal haemorrhage |  |
| Lethargy and drowsiness |  |
| Peripheral neuropathy | 'Japanese syndrome' (Waldenstrom et al., 1978) |
| Osteosclerosis |  |
| Hypertrichosis |  |
| Diabetes |  |
| Skin rashes; Erythema annulare | (Krook and Waldenstrom, 1978) |
| Pyoderma gangrenosum | (Moller et al., 1978) |
| Xanthomas | (Taylor et al., 1978) |
| Pruritus | (Erskine et al., 1977) |
| Yellow coloration of skin and hair | (Farhangi and Osserman, 1978) |

There is certainly no general agreement about diagnostic criteria for malignant multiple myeloma vis-a-vis non-malignant monoclonal gammopathy. The diagnostic criteria used, for instance, by the South-West Oncology Group (1975) accept a plasmacytosis of > 10 per cent in the bone marrow along with other features, while the Western Cancer Study Group (1975) accepts > 40 per cent plasmacytosis with other features.

We require a simple test to differentiate benign from progressive myeloma: studies of chromosome abnormalities (Liang and Roweley, 1978), depression of normal immunoglobulin levels (Peltonen et al., 1978), depression of circulating B lymphocyte numbers (Lindstrom et al., 1973) and the presence of Bence-Jones proteinuria (Hobbs, 1967) have not sharply differentiated the two. On the other hand, Cassuto et al. (1977) found good but not absolute distinction between myeloma and benign or reactive gammopathy by using bone marrow plasma cell acid phosphatase. Nevertheless, patients who have low levels of paraprotein (less than 35 g/litre IgG, 20 g/litre IgA) and borderline abnormalities in the bone marrow (50 per cent plasmacytosis) and who are without symptoms will have to be observed to see if their paraprotein level rises before therapy is instituted.

**Prognostic Factors**

**Staging by Cell Mass**

Several independent presenting features have been shown to correlate with survival in multiple myeloma and the 'cell mass' concept has been used to unify these factors into a staging system.

Durie and Salmon (1975) at the University of Arizona have calculated the cell mass in 71 patients based upon the equation

\[
\text{Cell mass} = \frac{\text{Total body } M\text{-component synthetic rate}}{\text{Cellular } M\text{-component synthetic rate}}
\]

The total M protein production rate depends upon height of the M band, plasma volume and the rate of catabolism of the paraprotein. The cell protein production rate is calculated by radioimmunoassay of in vitro paraprotein production by a sample of bone marrow containing a known number of plasma cells. In many tumours, prognosis depends upon the mass of tumour present and multiple myeloma is no exception. Calculated cell mass has been found to correlate with survival to a useful degree.

The next stage in the development of the staging system was to cross-correlate cell mass with various presenting features. This has enabled Durie and Salmon (1975) to develop a clinical staging system based upon the haemoglobin, serum calcium, size of the M band and the extent of lytic bone lesions shown by skeletal survey. The relevance of this staging system to prognosis is shown in Fig. 3 taken from clinical data alone at St Bartholomew's Hospital (Woodruff et al., 1978a). Further refinement of
Renal Function

The most characteristic renal lesion in multiple myeloma is irreversible chronic renal failure with tubular atrophy associated with acidification and concentration defects. Defronzo et al. (1978) have confirmed that this occurs in 40 to 50 per cent of patients at presentation and has corroborated the very close association between urinary light chain excretion and renal failure. There was some indication that lambda light chains were more nephrotoxic than kappa.

Both amyloidosis and Fanconi’s syndrome (phosphaturia, glycosuria, renal tubular acidosis and aminoaciduria) have been associated with lambda and kappa light chain excretion respectively (Fig. 4), sometimes over a long period and not associated with manifest myeloma (Kyle and Bayrd, 1975; Maldonado et al., 1975). Both conditions can occur in association with multiple myeloma, and a nice diagnostic problem might be created by a patient presenting with weakness, osteomalacia, and light chain excretion in the urine, where a diagnosis of Fanconi’s syndrome would indicate management different from that of multiple myeloma.

The staging system is required, since most patients fall into the high cell mass category and there is a need to discriminate further within this group.

Response to Therapy

This is the most important prognostic factor and the one that cannot be defined at the time of diagnosis (Durie and Salmon, 1975). A response to therapy (as defined by a reduction in the mass of paraprotein to at least half of the level at diagnosis) is an indication that the patient is likely to survive considerably longer than a similar patient who does not respond. The difference in median survival between the two categories was 28 months in the Alexanian et al. (1968) series, 12 months for non-responders and 40 months for responders. There is a weak correlation between high cell mass and failure to respond to treatment but, apart from this, it stands as an independent prognostic factor.

It would be very useful if response to therapy could be predicted at the time of diagnosis so that valuable time is not wasted on giving ineffective agents. An approach to this problem has been made in the University of Arizona (Hamburger and Salmon, 1977; Salmon et al., 1978) where soft-agar cultures of bone marrow myeloma cells are used to give a predictive test of sensitivity to cytotoxic agents. This test awaits development for routine use.

Age

Matzner et al. (1978) have made a useful contribution by emphasising the importance of age as a prognostic factor in multiple myeloma, older patients faring less well in their series. However, they do not provide the evidence for this as they do for other, less important, factors. They are not able to fit their data to the Salmon and Durie staging scheme, nor do they take account of the variable of ‘response to treatment’, which was shown to be of considerable importance in other series.

The various prognostic factors in myeloma are illustrated in Fig. 5. If a patient’s prognosis can be predicted, this will help in the following ways:

Fig. 5. Prognostic factors in multiple myeloma.

+ a = positive correlation. — a = negative correlation.

![Diagram of Prognostic Factors](image)

See also the table for a simplified view of the effect of light chains in renal function.
1. the physician will be able to plan the patient's management (both physical and psychological) with greater insight;
2. treatment may be intensified for the bad prognostic groups of patients if their general state is fair;
3. comparison between patients in different clinical trials will be possible by direct comparison of patients within the same prognostic group.

Therapy

Remission Induction

Oral melphalan or cyclophosphamide induce partial remission of myeloma in 50 to 60 per cent of patients (Bergsagel et al., 1967). Remission can be arbitrarily defined as reduction of the paraprotein to less than 50 per cent of pre-treatment levels, this being associated with pain relief and rise in haemoglobin. It is only rarely associated with recalcification of bone lesions or return of normal immunoglobulins.

The major benefit of intermittent oral therapy as opposed to continuous daily oral therapy lies in the reduced incidence of prolonged myelosuppression (Bergsagel et al., 1967). Since the demonstration of the equal efficacy of melphalan and cyclophosphamide (Medical Research Council, 1971) the choice between these two agents lies in their relative toxicities, which have not been fully evaluated; melphalan produces an increased incidence of leukaemia and sideroblastic anaemia (Gonzalez et al., 1977), while cyclophosphamide carries the risk of cystitis and possibly bladder carcinoma.

Addition of prednisolone to the treatment regime does not improve survival but is associated with more rapid reduction of paraprotein levels and rise in haemoglobin (Alexanian et al., 1969; Costa et al., 1973). There is a case to be made for the omission of prednisolone once remission has been achieved, since, with prolonged use, it may only increase osteoporosis.

Cycles of melphalan or prednisolone have been given six-weekly hitherto, in the belief that myelotoxicity is unacceptable with more frequent pulses. Our experience and that of the South-West Oncology Group has been that three weekly cycles are practicable and possibly increase the remission rate by increasing the dosage of melphalan that can be given per unit time.

Unless melphalan is given thoughtfully there is a risk that lack of response may occur because of underdosage. Alberts et al. (1978) showed that melphalan absorption is highly variable after administration of an oral dose. One patient showed no detectable melphalan for 24 hours after taking an oral dose under supervision. At St Bartholomew's Hospital the starting dose is 10 mg daily for four days repeated every three weeks, the dose being gradually increased until myelosuppression is seen, indicating that absorption is occurring.

The problem of non-compliance in drug taking has been scarcely entertained in medical oncology, since most drugs are given intravenously under supervision. Smith et al. (1977) showed that 11 of 30 (36 per cent) patients with acute lymphoblastic leukaemia were not taking their maintenance therapy. It is likely that older patients with multiple myeloma may fail to realise the importance of regular melphalan treatment or they may simply forget to take it. Alternatively, non-compliance may have some more complex cause, and it may partly explain the relatively low response rate seen in this disease.

Intravenous administration of melphalan is probably unnecessary; it is painful, costly and dangerous. Severe myelosuppression may be seen with doses that are harmless when given orally.

The possible enhancement of melphalan toxicity in the presence of renal failure is an important practical question, as about 50 per cent of patients present with this problem. Alberts (1978) has shown that some myelotoxic melphalan metabolite is retained in nephrectomised dogs. Where the possible risk of such melphalan toxicity exists, dosage should be halved or, perhaps a more satisfactory alternative, cyclophosphamide, should be substituted.

Remission Maintenance Treatment

It is possible to take either of two attitudes to remission maintenance treatment. It could be suggested that this is the time when further manoeuvres to reduce cell mass to zero would have most effect, but in practice this has been tried using cycle active agents it has not been successful (Alberts et al., 1977). There is a contrary case to be made for minimising treatment in remission since it is then that patients are enjoying their best health during the induction-remission-relapse cycle.

All patients with myeloma will relapse after partial remission. The median duration of remission was found to be 9 months, followed by relapse with a median doubling time of 2.6 months. Theoretically, if maintenance treatment is withheld, patients may relapse more quickly but they could be more sensitive to further chemotherapy. In practice, Alexanian et al. (1978) found no significant difference in survival in patients maintained after 12 months with either melphalan, prednisolone, BCNU, or no treatment. It does seem possible to leave patients without treatment after 12 months, particularly when the M band has fallen to undetectable levels (Alexanian et al., 1978) but this is acceptable only if the patients are followed very closely to detect relapse. It is, however, revealing that the latest South-West Oncology Group trials do not include a ‘non-treatment’ category.

Relapse

A major challenge in multiple myeloma is presented by the fact that in addition to failing to clear the tumour during remission induction and maintenance, the tumour eventually becomes resistant to the first-line alkylating agent. The mechanism by which resistance to alkylators occurs is not known. It has been suggested (Alexanian et al., 1977a) that resistant stem-cells are present from the start of treatment and these gradually take over from the sensitive cells. It seems likely that there is a whole range of sensitivities to an alkylating agent
within the tumour, and the residual tumour mass in remission is still turning over rapidly but is maintained at low levels by repeated exposure to alkylating agents. Myeloma in partial remission may be considered the ideal system to select out a resistant clone since it is probably rapidly dividing, periodically exposed to a strong selective force by the administration of alkylating agents, and also exposed to a potent mutagen in the form of the alkylator.

The cellular mechanisms by which myeloma cells resist alkylating action are not known, but it has been shown in the mouse plasmacytoma that resistance to an alkylating agent can be overcome by chloroquine (Gandin and Yielding, 1969), which is an inhibitor of DNA repair. This is one mechanism that may be important in man, although Kyle et al. (1975) found no benefit from added chloroquine in a clinical trial. DNA repair may, however, be occurring, and it is possible that the high DNA labelling index seen in the early phase of myeloma treatment may be partly due to extensive DNA repair occurring in plasma cells whose DNA has been alkylated.

Two forms of therapy have been devised for patients relapsing with multiple myeloma. Bergsagel et al. (1972) reported a good response in 6/19 patients with myeloma relapsing on melphalan and prednisolone, using cyclophosphamide 1 g/m² given orally over 4 days or intravenously in a single dose, every three weeks, while Alberts et al. (1976) reported improvement in 7 of 13 patients relapsing from alkylator/prednisolone therapy using doxorubicin (adriamycin) 30 mg/m² and BCNU (1.3 di (2 chloroethyl) 1. nitrosourea) 30 mg/m² i.v. every three weeks. Thus, myeloma is not universally resistant to alkylator therapy in relapse, and in suitable, fit patients it is justified to administer 'second-line' therapy since useful prolongation of life may be seen. It is obviously important to detect relapse as early as possible by serial paraprotein estimates, to prevent irreversible bone damage before second-line treatment is instituted.

Buonanno et al. (1978) reported the results of treating relapsing or non-responsive patients with multiple myeloma with a multiple drug (M2) regime consisting of melphalan, cyclophosphamide, vincristine, BCNU and prednisolone. They saw a response in 9 of 12 patients with remissions lasting up to 14 months. The use of such a large number of drugs could be criticised, especially as they were using melphalan again in patients who had already received this drug, while not using adriamycin in the regime, an active agent that the patients had not previously experienced.

Multiple Agent Chemotherapy

Since life-expectancy can be increased by the use of second-line agents in relapsing patients, it is reasonable to suggest that, as early relapse is undesirable, it may be possible to delay relapse by giving second-line agents along with 'first-line' drugs from the start of treatment as quadruple or even quintuple chemotherapy. This is analogous to the use of quadruple chemotherapy for Hodgkin's disease (Nicholson et al., 1970) although the age of the patients and their condition obviously different.

Two major centres in the USA are studying multiple drug therapy for myeloma. The South-West Oncology Group reported the results of quadruple therapy with combinations of vincristine, BCNU, cyclophosphamide, melphalan and prednisolone (Alexanian et al., 1977b, c) and conclude that the combinations containing vincristine show superior remission rates and survival to those which do not. These conclusions are open to criticism, in particular since the interval between treatments was three weeks in the vincristine-containing regimes and four weeks in the non-vincristine regimes. The dose of drug per unit time could explain the differences seen. As reported in 1977, the difference between median survival of vincristine-containing and non-vincristine-containing regimes could be about 10 months, but a non-vincristine-containing regime, melphalan, cyclophosphamide, BCNU and prednisolone, appears to be producing equally good results. Further studies now in progress in the South-West Oncology Group should give more definite answers to the question of the value of multiple drug therapy.

The Sloan-Kettering group (Case et al., 1977) have reported the interim results of an intensive regime using melphalan, cyclophosphamide, prednisolone, BCNU and vincristine and have compared the survival with a retrospective group of patients receiving melphalan and prednisolone alone. They found a statistically significant improvement in survival on the intensive regime, with a projected median survival of about 50 months. These impressive results are achieved at the cost of giving intravenous cyclophosphamide (700 mg for a 70 kg man) and BCNU (35 mg for a 70 kg man) every five weeks. The regime does not make use of the synergism of BCNU and adriamycin. Nausea and vomiting were recorded with the regime; the occurrence of alopecia was not mentioned.

It is important to emphasise that these results are preliminary and we consider that treatment with multiple agents is not an established form of chemotherapy for myeloma.

Localised Plasmacytoma

Although localised plasmacytoma may occur in all parts of the body, the prognosis differs according to the site. Hence Woodruff et al. (1978b) re-emphasised the good prognosis of soft tissue plasmacytoma occurring around the nose and mouth. Sixteen patients were successfully treated with local radiotherapy in a dose ranging from 1250 to 5000 rad, local recurrence taking place in only one patient and generalised recurrence in one patient with plasmacytoma of the tongue.

The difficulty of demonstrating that a bony plasmacytoma is truly localised is identical with the problem of differentiating benign from malignant gammopathy. Most solitary bone plasmacytomas progress to generalised myelomatosis. The prognosis in any series of 'solitary plasmacytomas' of bone will depend upon the intensity with which generalised disease is excluded at diagnosis. Kaplan and Bennett (1968) reported a patient with localised vertebral plasmacytoma who had a paraprotein that became undetectable after local
irradiation with 5000 rad and the patient remained well for at least eight years. This is exceptional; Conkin and Alexanian (1975) reported progression in 12 of 16 patients with localised plasmacytoma of bone within one year of diagnosis.

Supportive Care

The importance of radiotherapy in pain relief and spinal cord decompression does not need emphasising. It is interesting to note that the site of pain may precede demonstrable lytic bone lesions, and the speed of pain relief after radiotherapy suggests that the pain is not produced simply by mechanical distortion. Osteoclastic activity in myeloma is probably stimulated by an osteoclast activating factor that is distinct from parathormone and prostaglandins, and is probably identical to a lymphokine produced by normal stimulated lymphocytes (Cohen, 1977). It is possible that pain is mediated by a similar lymphokine directly stimulating pain receptors in or near bone. Radiotherapy may be particularly good at inhibiting production of these factors.

Benign Monoclonal Gammopathy

Benign monoclonal gammopathy requires close definition and can be considered the finding of a paraprotein in a patient who is otherwise free of detectable disease. Paraproteins have been detected in patients with primary amyloid (Kyle and Bayrd, 1975), Fanconi’s syndrome (Maldonado et al., 1975), carcinoma (Ameis and Puzanski, 1975), polyneuropathy (Waldenstrom, 1973), autoimmune disease, lymphomas (Alexanian, 1975), and infections (Groshong et al., 1976). By the above definition they do not have a benign monoclonal gammopathy. Waldenstrom (1973) reviewed the findings from several surveys and found benign monoclonal gammopathy in between one and three per cent of people, the incidence rising with age. It is important to know what will happen to such people; Axelsson and Hallen (1968) surveyed 64 patients with benign monoclonal gammopathy, and after five and a half years it was possible to re-examine 39. Two patients had shown a significant rise in their M band but none had developed multiple myeloma.

Hyperviscosity

The Westminster Hospital groups (Preston et al., 1978) have demolished the view that hyperviscosity is rare in multiple myeloma. They found clinically important hyperviscosity in 11 out of 84 (13 per cent) of their patients, occurring most commonly with IgA or IgG, myeloma. Hyperviscosity is more common with paraprotein levels above 40 g/litre (Alexanian, 1977), but in some cases polymerisation of immunoglobulins increases viscosity more than would be expected for a particular level of paraprotein.

It is generally believed that plasmapheresis is of little value to decrease viscosity in IgG or IgA myeloma because of the probability that extravascular immunoglobulin will promptly return into the vascular compartment. In cases where immunoglobulin dimers and trimers are contributing to hyperviscosity, plasmapheresis should remove these and reduce viscosity for some time.

Acknowledgements

D.P. was a visiting research fellow to the University of Arizona Health Sciences Center, Tucson, Arizona, and acknowledges the co-operation of Dr S. E. Salmon, Dr Brian Durie, Dr David Alberts and Dr Anne Hamburger. The fellowship was funded by the Imperial Cancer Research Fund. The authors also acknowledge helpful discussions on the cellular immunology of myeloma with Dr John Habeshaw.

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**Dorchester's Catalogue**

The Marquess of Dorchester's library is the basis and chief glory of the College library. Unlike his father who was arrested as a Royalist, he seems to have spent his time during the Civil War browsing in his library and yet was acceptable to Charles II at the restitution of the monarchy. Soon after, in 1664, he had a manuscript catalogue made of his library. This is now in the College library, although the Dorchester library itself did not come to the College until after the Marquess's death in 1680. The catalogue was compiled by Thomas Salusbury, a graduate of Trinity College, Dublin. A scholar and mathematician, his life was ruined by the Civil War. As a Royalist he fled to Europe, returning in 1654 to be arrested. A year after completing his catalogue he died of the plague. But he did manage to publish two volumes of *Mathematical Collections and Translations* (1661 and 1665). These included a translation of Galileo's *Discourse*. To continue the story of ill luck, almost all the stocks of these volumes were destroyed in the Great Fire of London. The College has recently been given a superb facsimile of the two volumes, the generous gift of Mr Jacob Zeitlin of Los Angeles. He, together with Dr Gibson of Vancouver, was instrumental in arranging the return to this country of the Rolls Park portrait of William Harvey. Mr and Mrs Zeitlin visited the College last year for the Harveian celebrations. The Salusbury volumes were a memento of the visit and the details of Salusbury's life were discovered by Mr Zeitlin, who found a collection of Salusbury's letters. The College is fortunate to have such friends.