Current Practice

Management of Multiple Myeloma

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Considerable progress has been made in the therapy of multiple myeloma, and it is now possible not only to alleviate symptoms but to prolong survival. Patients may be enabled to resume full activity—or at least to lead a limited but comfortable existence.

Multiple myeloma is a malignant disease of plasma cells, occurring usually in middle-aged and elderly people, and characterized by a proliferation of plasma cells throughout the bone marrow and lymphoreticular tissue. Occasionally it may start as an isolated tumour mass, but generalization of the disease inevitably occurs in time. When the disease progresses bone marrow failure, bone destruction, increased susceptibility to infection, and metabolic disturbances such as hypercalcaemia, hyperuricaemia, and uraemia may arise as complications. The disease is invariably fatal.

The diagnosis of multiple myeloma and the clinical and pathological features of the disease have been extensively reviewed,[1–4] and will not be considered in detail. The diagnosis is based on the demonstration on serum electrophoresis of an homogeneous band of protein, the so-called paraprotein or "M" component, or the presence of plasmacytosis with bone destruction apparent on a radiological survey of the skeleton, or the presence of a solitary tumour composed of myeloma tissue. Usually there is no difficulty in distinguishing the abnormal plasma cells seen in myeloma tissue, but occasionally difficulty can be experienced, and care must then be taken that the plasmacytosis is not the result of drug sensitivities, diseases of collagen tissue, chronic infection, cirrhosis of the liver, or malignant disease such as carcinomatosis or Hodgkin's disease. In the same way homogeneous bands or "M" components on serum electrophoresis do not necessarily denote myeloma: they may be seen in macroglobulinaemia or other more benign immunoglobulin disorders.

Clinical Pathology

Tests carried out on the serum and urine are an essential part of diagnosis, and they may also provide evidence which will be of value in management and prognosis.

Serum and Urinary Proteins.—Gitlin[5] and Cohen[6] have reviewed the terminology of the immunoglobulins. Most paraproteins found in multiple myeloma are related to the γG and γA immunoglobulins. More rarely paraproteins related to γM and γD immunoglobulins are found, and in about 6% of a large series Hobbs[7] found that the myeloma was producing only Bence Jones protein (B.J.P.)—that is, the light chain moiety of the immunoglobulins. The prognosis for patients producing γG and γA paraproteins does not seem to differ. Though very few cases of γD paraproteins have been recorded their survival appears to be short.

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Certain complications appear to be more common in the presence of certain paraproteins. Thus γG myeloma is associated with a higher incidence of infection and with less frequent occurrence of hypercalcaemia.[8]

The presence of Bence Jones protein is of considerable prognostic importance. The light chain moieties which form B.J.P. are of two types, kappa (κ) or lambda (λ) chains. Hobbs[9] investigated a series of patients with paraproteinaemia and showed that the presence of B.J.P. in excess of 1 mg./100 ml. in the urine indicated a bad prognosis. Earlier, Waldenström[10 11] had shown that the occurrence of B.J.P. together with a rising level of paraprotein in the serum was also a bad augury.

The presence of B.J.P. is closely correlated with renal failure and with anaemia, both of which have an adverse effect on survival.[8 12] Bergsagel, Migliore, and Griffith[13] reported a higher incidence of response to therapy in patients producing B.J.P. of type κ. Caggiano, Cuttner, and Solomon[4] were unable to confirm this, but further evidence is now available from the M.R.C. trial in which patients producing κ light chains appear to have a somewhat better prognosis.[14] In a long-term study by the South-west Cancer Chemotherapy Group patients producing λ chains have a higher incidence of renal failure, a poorer response to therapy, and a shorter survival.[15]

Renal Function.—Between a third and a half of the patients who die from multiple myeloma do so as a consequence of renal failure. Many mechanisms contribute to the failure, including pyelonephritis, nephrocalcinosis, intracellular tubular damage, and amyloidosis. Once renal failure has begun in myeloma current forms of therapy do not appear to be able to arrest it. A patient with a blood urea of over 80 mg./100 ml. has a poor prognosis. The median survival of patients in this group is about eight weeks. This compares with a median survival of over three years for the group with blood ureas of less than 80 mg./100 ml.[8]

An elevated level of serum calcium has been noted in a fifth to a half of patients when they first presented.[3] Though increased bone resorption is the main factor responsible, widespread bony erosions are not always present. The serum alkaline phosphatase is usually not raised in multiple myeloma. It does not appear that hypercalcaemia has any effect on prognosis.

In common with many malignant processes hyperuricaemia and secondary gout may be associated with multiple myeloma.

Haematological Studies.—Anaemia frequently complicates the disease. When the anaemia is severe and requires frequent blood transfusion for its correction the patient's prognosis is poor. The mechanism for the production of anaemia in myeloma is complex. In a comprehensive investigation Cline and Berlin[16] showed that anaemia could be due to bone marrow failure, shortening of the red cell survival, and iron deficiency. The latter usually resulted from recurrent bleeding episodes associated with thrombocytopaenia, and was usually seen in the later stages. Megaloblastic changes have been found on

bone marrow examination by a number of investigators. Thirty-two patients with myeloma were studied by Hoffbrand, Hobbs, Kremenchuzky, and Mollin,[17] and intermediate megaloblastic changes were noted in six. These changes were mainly due to folic acid deficiency. Addisonian pernicious anaemia is rare in myeloma ; the low vitamin B_{12} levels that have been recorded were related to a reduction in the normal circulating immunoglobulin levels.

Treatment

Waldenström[18] has outlined the basic principles of therapy in myeloma. Firstly, the treatment of a generalized malignant disease must be systemic and should not be directed against local lesions. Secondly, he has drawn an analogy between the disease and an infection with a microorganism. The cytostatic drug, like an antibiotic, must be given initially in high concentration and then a lower dose must be given continuously. The specific chemotherapy available and its administration will be discussed in detail later. Supportive care to prevent or relieve complications such as fractures, infections, hypercalcaemia, hyperuricaemia, renal failure, and hyperviscosity will be dealt with first.

Supportive Therapy

Skeletal pain is often responsible for the patient leading a limited existence. Deep *x*-ray therapy of local skeletal deposits is often of great benefit. Though the rapid development of chemotherapy has done much to make long-term control of skeletal pain easier, deep *x*-ray therapy is very effective when pain originates from a myelomatous deposit. It has the great advantage of providing rapid relief. Relief is usually so complete that if pain persists it may be advisable to seek some other cause for its occurrence, such as an unrecognized pathological fracture. Deep *x*-ray therapy may also be particularly useful when a deposit within the spinal theca threatens damage to the spinal cord.

Immobilization of pathological fractures and spinal support by corsets and steel braces may bring relief of pain. The use of sodium fluoride to produce subacute fluorosis with hardening of the skeleton is not justifiable because of the risk of retinal damage.[19]

Infections are frequent in myeloma, and chest infections seem particularly common. They require urgent and adequate therapy. Because of the reduction in the level of normal immunoglobulin that is seen as myeloma progresses,[9] these patients often show poor resistance to infection, but prophylactic administration of gammaglobulin seems to be disappointing.

Slight hypercalcaemia may be treated by rehydration and specific chemotherapy. When hypercalcaemia is more pronounced and symptoms such as nausea, vomiting, or mental disturbances supervene, immediate administration of corticosteroids is imperative. A dramatic improvement is usually seen.

Hyperuricaemia may occur in the absence of renal failure. Treatment with allopurinol has been reported and is effective.[20]

The renal failure of myeloma is usually chronic and irreversible. Acute renal failure may also occur. This may happen spontaneously or follow periods of vomiting with consequent dehydration. Vomiting may be induced by specific therapy with urethane or melphelan.

There are a number of reports of acute renal failure after pyelography. This may occur with recently introduced contrast media as well as with established media.[21] Renal failure occurs too frequently to be a coincidence, but it is still a relatively rare occurrence. Vix[22] carried out 52 intravenous pyelograms in 40 patients without any evidence of renal deterioration, even in those already suffering from chronic renal failure. Pyelography should nevertheless not be carried out without a good indication, and if an intravenous pyelogram is necessary it is wise to omit the period of dehydration that is part of the routine preparation.

A marked increase in the viscosity of serum may be seen occasionally in patients with γG myeloma. Hyperviscosity may give rise to mental symptoms very similar to those observed in hypercalcaemia, and, in addition, a retinopathy, recurrent bleeding, cardiac failure, and lassitude may occur. Smith, Kochwa, and Wasserman[23] were able to demonstrate the formation of aggregates of γG in vivo. As retinal damage may rapidly progress to blindness plasmaphoresis must be carried out urgently to reduce the circulating protein. Plasmaphoresis must be followed by specific chemotherapy.

There are a number of causes for the bleeding diathesis seen in some patients with myeloma. Thrombocytopenia may result from bone marrow failure or from treatment with cytotoxic agents. The platelets may become coated with abnormal protein,[24] and rarely a circulating anticoagulant may cause bleeding.

Myeloma is a disease of late middle age, so that the management of pregnancy occurring with this condition is uncommon. Occasionally, however, myeloma occurs in children or young adults, and Kosova and Schwartz[25] reported the case of a 35-year-old woman with myeloma who, following a remission induced with deep *x*-ray and urethane, had a normal pregnancy and delivery. Pregnancy did not seem to cause a deterioration of her condition.

Specific Therapy

Many drugs have been used in the treatment of myeloma. Some drugs such as stilbamidine, methotrexate, vinblastine, and hydroxyurea have been shown to be ineffective. Others, like urethane and corticosteroids, may produce both subjective and objective improvement, but have not been shown to increase the length of survival. In a study by Holland *et al.*[12] urethane was shown to be of no greater benefit than a placebo in increasing survival, and patients treated with it survived for a shorter period than those treated with supportive therapy only.

After extensive trials[11 26] cyclophosphamide and melphalan have been shown to be effective in treatment and to produce a definite increase in survival. It is difficult to compare the length of survival seen in recent series of patients treated with these alkylating agents with the series reported more than a decade ago. Some of the early series reported a median survival of only three months ; Osgood[27] showed in 1960 that the median survival for patients treated with steroids, radioactive phosphorus, and urethane was 20 months. This improvement was probably related, however, to the earlier recognition of the disease in the later series.

Korst *et al.*[28] reported a series of 165 patients treated with cyclophosphamide. The median survival of this group was 32 months, compared with 9 months in an ancillary group treated without cyclophosphamide. In 82 patients treated with melphalan over a seven-year period Alexanian *et al.*[29] showed a median survival time of 34 months. Furthermore those who responded to melphalan lived some 30 months longer than a group of non-responders. There seems to be no doubt that cyclophosphamide and melphalan do prolong survival. In the M.R.C. trial[8] comparing them no significant difference between them was shown.

Dosage and Toxic Side-effects

Cyclophosphamide

This alkylating agent is activated in vivo. It can be given orally or intravenously, but when treating myeloma the oral

route is usually preferred. It produces improvement in about a third of patients treated.[3] The dose is 2 mg./kg./day, but the daily dosage is varied to avoid bone marrow suppression. Besides marrow toxicity cyclophosphamide can cause alopecia and haemorrhagic cystitis. Continued chemotherapy should be attempted, and an examination of the white cell count and platelet count should be carried out every three to four weeks.

Melphalan

Phenylalanine mustard can also be given orally. When first introduced for the treatment of myeloma it was suggested that a dose of 0·15 mg./kg./day should be given for a week followed by a period in which the bone marrow recovered. Maintenance therapy was then continued with doses of 0·05 mg./kg./day. Long-term therapy was carried on with doses not greater than 0·06 mg./kg./day.[10 26 30] Toxic effects include nausea, vomiting, ulceration of the mouth, gastro-intestinal haemorrhage, and bone marrow depression. Melphalan should be given with great care in the presence of renal failure.

The number of patients who show a response to either cyclophosphamide or melphalan is still disappointingly low. Efforts have been made therefore to improve the remission rate and prolong survival by altering the regimens of administration or using combination chemotherapy with corticosteroids as well as cytostatic drugs. Alexanian *et al.*[15] have compared four treatment regimens, daily melphalan 0·025 mg./kg./day, intermittent melphalan 0·25 mg./kg./day for four days followed by an interval of six weeks, intermittent melphalan with prednisolone 1·0 mg./kg. on alternate days, and intermittent melphalan with prednisolone 2·0 mg./kg./day on the days when melphalan is being administered. They found that objective responses to melphalan occurred more often when it was given intermittently, and that there was no indication of increased toxicity.

The addition of prednisolone to the regimen resulted in an enhanced response, with some 70% of the patients responding, and the median survival of the group treated with melphalan and prednisolone was six months longer than the group treated with melphalan alone. It was also evident that some patients who had shown no signs of responding to melphalan would do so when prednisolone was added.

Recent advances such as these in the therapy of myeloma may now perhaps form the basis for a more generally optimistic outlook in this condition.

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REFERENCES

1 Osserman, E. F., and Takatsuki, K., *Medicine (Baltimore)*, 1963, **42**, 357.
2 Drivsholm, A., *Acta Medica Scandinavica*, 1964, **176**, 509.
3 Bergsagel, D. E., Griffith, K. M., Haut, A., and Stuckey, W. J., *Advances in Cancer Research*, 1967, **10**, 311.
4 Caggiano, V., Cuttner, J., and Solomon, A., *Blood*, 1967, **30**, 265.
5 Gitlin, D., *Annual Review of Medicine*, 1966, **17**, 1.
6 Cohen, S., *British Journal of Haematology*, 1968, **15**, 211.
7 Hobbs, J. R., *Scientific Basis of Medicine Annual Reviews*, 1966, p. 106.
8 Galton, D. A. G., and Peto, R., *British Journal of Haematology*, 1968, **15**, 319.
9 Hobbs, J. R., *British Medical Journal*, 1967, **3**, 699.
10 Waldenström, J., *Acta Medica Scandinavica*, 1964, **176**, 345.
11 Waldenström, J., *British Medical Journal*, 1964, **1**, 859.
12 Holland, J. F., *et al.*, *Blood*, 1966, **27**, 328.
13 Bergsagel, D. E., Migliore, P. J., and Griffith, K. M., *Science*, 1965, **148**, 376.
14 Hobbs, J. R., *British Journal of Haematology*, 1969, in press.
15 Alexanian, R., *et al.*, *Journal of the American Medical Association*, 1969, in press.
16 Cline, M. J., and Berlin, N. I., *American Journal of Medicine*, 1962, **33**, 510.
17 Hoffbrand, A. V., Hobbs, J. R., Kremenchuzky, S., and Mollin, D. L., *Journal of Clinical Pathology*, 1967, **20**, 699.
18 Waldenström, J., *British Journal of Haematology*, 1968, **15**, 217.
19 *British Medical Journal*, 1967, **2**, 128.
20 Rundles, R. W., *Annals of the Rheumatic Diseases*, 1966, **25**, 615.
21 Gross, M., McDonald, H. M., and Waterhouse, K., *Radiology*, 1968, **90**, 780.
22 Vix, V. A., *Radiology*, 1966, **87**, 896.
23 Smith, E., Kochwa, S., and Wasserman, L. R., *American Journal of Medicine*, 1965, **39**, 35.
24 Vigliano, E. M., and Horowitz, H. I., *Blood*, 1967, **29**, 823.
25 Kosova, L. A., and Schwartz, S. O., *Blood*, 1966, **28**, 102.
26 Speed, D. E., Galton, D. A. G., and Swan, A., *British Medical Journal*, 1964, **1**, 1664.
27 Osgood, E. E., *Cancer Chemotherapy Reports*, 1960, **9**, 1.
28 Korst, D. R., Clifford, G. O., Fowler, W. M., Louis, J., Will, J., and Wilson, H. E., *Journal of the American Medical Association*, 1964, **189**, 758.
29 Alexanian, R., Bergsagel, D. E., Migliore, P. J., Vaughn, W. K., and Howe, C. D., *Blood*, 1968, **31**, 1.
30 Hoogstraten, B., *et al.*, *Blood*, 1967, **30**, 74.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in common use.

Androgens and Anabolic Steroids

Several androgenic steroid hormones are secreted by the adrenal cortex and the testis ; the most powerful is testosterone. The action of these hormones is most clearly seen in the changes that occur in boys at puberty. Under the stimulus of gonadotrophin secreted by the pituitary gland testosterone and other androgenic steroids are secreted in significant amounts for the first time. These hormones are responsible for changes in the larynx causing deepening of the voice, for growth of the external genitalia and the prostate, and for the appearance of body hair with the typical male distribution. They also produce pronounced retention of nitrogen and the build-up of body protein which results in development of the musculature and also accounts for, at least in part, the spurt in growth at puberty. As well as stimulating growth the androgenic hormones cause maturation of the bones and, eventually, fusion of the epiphyses, which brings growth to a halt. It is the property of these hormones to produce nitrogen retention and encourage protein anabolism which has led to a large scale attempt to develop compounds that will retain these actions but not have the masculinizing effects. These anabolic steroids are tested by bioassays which separate the effect upon nitrogen metabolism from the androgenic effects. Many such compounds have now been produced in which the nitrogen retaining properties predominate over the androgenic effects. None, however, has yet been shown to be entirely free of androgenic actions when tested in man.

Hypogonadism

The most clear-cut indication for the use of testosterone is as replacement therapy in patients with hypogonadism. This may be due either to disease of the testis or to diminished